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STALKERS OF PESTILENCE

WADE W. OLIVER

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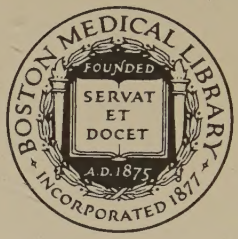

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RIDERS OF THE PLAGUES: The Story of the Conquest of Disease. By JAMES A. TOBEY. Scribners. 1930. $3.50.

STALKERS OF PESTILENCE: The Story of Man's Ideas of Infection. By WADE W. OLIVER, M.D. New York: Paul B. Hoeber. 1930. $3.

THESE two books offer a marked contrast in regard to the method of depicting the same story. Both deal with the development of our ideas of sanitation and public health from the earliest times to the present. Dr. Tobey, a doctor of public health, writes the larger book, in the more popular style. There are excellent chapters on the early great plagues of the past; Pasteur and his development of bacteriology; the conquest of yellow fever, especially by physicians connected with the United States Army; the new science of sanitation, and Trudeau and tuberculosis. The story is told in an interesting way, but the book is so hastily put together and marred by such atrocious English, that in many places the author's meaning is entirely obscured by his apparent inability to write a simple English sentence.

Oliver's book, on the other hand, is much smaller and less pretentious, but it is well written and is a true scientific contribution to the history of medicine, at the same time being sufficiently popular in type to appeal to the average reader. Oliver also has given careful attention to references in the literature. His book, which has already appeared in parts in the *American Journal of Surgery* for 1929, can be most highly recommended.

Saturday Review 10/25/30

STALKERS OF PESTILENCE

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TO MY FATHER

PREFACE

For untold generations, the lean and terrifying shadow of infection has fallen across the affairs of men. Since earliest recorded history, disease has incalculably shaped the destiny of mankind; individuals, communities, races have been stamped by its malign impress. Great epidemics have swooped down upon man with fearsome speed; he has seen his strongest, as well as his weakest, go down before the common enemy of mankind.

During the reign of Justinian almost fifty per cent of the entire population of the Roman Empire perished from plague. And it was this same "Black Death" which swept over Europe during the fourteenth century and snuffed out almost twenty-five million lives. It was Ross who suggested that malaria, endemic in Italy for centuries, may have been the main contributing cause of the downfall of ancient Rome.

Who knows how much Napoleon's illness during the battle at Waterloo molded the history of the Western World; what undiagnosed imbalance of glands of internal secretion may have contributed to the shaping of a Calvin, a Schopenhauer? Out of a crop of boils sprang the immortal lamentations of Job; up from the lines of Keats' immortal songs shudders his racking,

consumptive cough. Truly Disease, marshal of the hosts of death, has incalculably influenced mankind; in man's upward struggle through the long aeons, illness has forever dogged his footsteps.

It is the purpose of this volume briefly to trace the historical development of man's ideas of the nature of infectious diseases. At the outset, the fact is developed that disease probably ante-dates man by millions of years. Lesions indicative of pyorrhea alveolaris have been discovered in the jawbone of a prehistoric three-toed horse; cave bears of the Pleistocene period apparently were subject to arthritis deformans, a severe form of rheumatism. Then follows an attempt to unfold the ideas of infection held by the ancient Egyptians and Babylonians and Hindus, and other ancient peoples. Next the story leads us through ancient Greece and Rome, and ancient China and Arabia, then to the Medieval Period and the Renaissance, on through the seventeenth, eighteenth, and nineteenth centuries, and up through the first quarter of our own twentieth century. Great, commanding figures arise; great errors, great truths are promulgated; superstition and magic wage their immemorial strife with clear-eyed reasoning and accurate observation. A strange, human drama it is, this struggle of the human mind to comprehend and analyze the nature of disease, its secret nemesis which

walks in darkness and takes its ruthless toll of living, breathing bodies and thinking, dreaming brains.

WADE W. OLIVER.

Brooklyn, N. Y.
July, 1930.

FOREWORD

The implied intent of a foreword is to whet the appetite for what is to be found in the pages that follow. These pages are to be welcomed for the warp of human disease in the fabric of civilization is not as a rule conspicuous in history as written and taught. Wars have guided the pen of historians and other phenomena have followed limpingly. Indeed a perusal of many texts gives the impression that war was the sole occupation of humanity before our present era. We are left to imagine whence came the energy to conduct wars and how the remainder of the population not on the war path managed to exist.

The desire to know something of the evolution of medical theories and practices comes to all students of disease sometime when they have been fortified by a fair understanding of the theory and practice of their own time. The lives of the originators and exponents of epochal changes, or whatever fragments of such lives have escaped the destructive tendencies of man and time, will be of interest even to those who will not attempt to live themselves through exhaustive study and research into the periods of quiet between the births of revolutionary ideas. The volume before us is a good introduction for such inquisitive minds. It gives the reader a brief account

of the chief periods when medicine turned a sharp corner. The causes of the long delays intervening between these turns on the traveled road may well occupy the reader and by linking them with political, military, religious and social events and crises he will form an intellectual background well worth constructing. He will note that in the period within the memory of those living medicine took a sharp turn during the lives of Pasteur and Koch and that what has followed is largely the unfolding of the new relations pointed out by them.

The author has taken an eclectic course in not only focusing on the epochs introduced by new ideas in medical theory but also in outlining the lives of the great physicians and medical radicals. These, through their observations and researches, reached conclusions which upset traditions and beliefs and gave offence to powerful, entrenched groups and castes. He has not dealt with the pestilences that raged through the ancient and the medieval world, because they need detailed reading and study for which many good books are within reach.

Medical history is of far less importance as a disseminator of light on current problems of disease than as an interpreter of the ups and downs of human fortunes and as a softener of the bias which comes from stereotyped instruction when past

history is viewed chiefly from the standpoint of martial activities or religious constraints and inhibitions. Disease, in the form of plagues and pestilences, appears to have been the biological factor most powerful in controlling the growth of civilization.

In these pages the student will get a glimpse of various interesting psychic phenomena. He will note the theory and practice of medicine beginning in superstitions and mythology involving the entire universe, coming gradually into material proximity to man, i.e. in the atmosphere in miasmas, earthquakes, witches, poisoners, and the like, thence to an understanding of the living causes of disease, visible and invisible to the naked eye, which we know as parasites. He will note the tenacity with which false ideas of disease were held and the frequently resulting extreme injustice and cruelty practiced by men on their own kind. He will note how innocent beings can be accused, tortured and killed on the basis of wholly false beliefs concerning the causes of disease. He needs to draw the lesson of the danger confronting society today in the suppression of freedom of teaching and speech by the majority which theoretically at least is always a mob.

An interesting side light is cast on the progress of medical enlightenment by the tenacious life of medical texts. Galen's writings remained standard for over a thousand years. One text of the 17th

Century is reported as having served its purpose for fifty years. Today a medical text is outworn in five years. If the reader ventures to look into original documents he will note the wordiness and deliberation of earlier writers as compared with the word-sparing assertions of the present. And with this change he will note that that prolonged rationalizing about dubious observations disappears with fact-gathering and experiment.

Coming fresh to the task, the reader will marvel at the stagnation of the human mind through centuries with new, stimulating, reconstructive ideas within reach. He may be induced to continue his studies to find some answer to the questions that suggest themselves in view of this anomalous behavior. Was it the great waste of labor involved in more primitive living? Was it perverted religious concepts, a dominating military spirit, government by a privileged class, the frequency of epidemic disease and pestilence? These queries would keep his leisure occupied with a study of past events and perhaps incidentally develop some apprehensions for the future.

It is to be hoped, that with these possibilities in mind the reader will go over the text of Dr. Oliver's presentation. His discussions and annotations indicate a work of love rather than the desire to add another volume to the yearly stream. Per-

haps the reader will not stop but attack the larger, more detailed histories, which the author has taken pains to quote in his copious list of references.

THEOBALD SMITH.

Princeton, N. J.
June, 1930.

CONTENTS

Page

Preface vii

Foreword xi

List of Illustrations xvii

Chapter

I. Prehistoric Man to Hippocrates. 1

II. Arabic Medicine, The Medieval Period & The Renaissance . . 49

III. The Seventeenth and Eighteenth Centuries. 89

IV. The Nineteenth Century 150

V. The Twentieth Century. 211

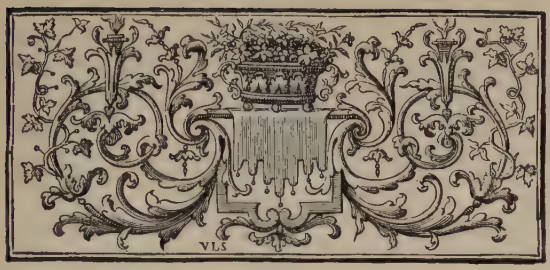
References 227

Index of Personal Names. 235

Index of Subjects 240

LIST OF ILLUSTRATIONS

Figure		Page
1.	Hippocrates. (460–370 B.C.)	23
2.	Galen. (130–200)	41
3.	Paracelsus. (1493–1541)	64
4.	Girolamo Fracastaro. (1483?–1553)	70
5.	Andreas Vesalius (1514–1564) dissecting a body in secret	75
6.	Michael Servetus. (1509–1553)	78
7.	Ambroise Paré. (1510–1590)	80
8.	William Harvey. (1578–1657)	91
9.	First pictorial representation of bacteria. Leeuwenhoek, 1683	98
10.	Lazzaro Spallanzani. (1729–1799)	124
11.	Sir Isaac Newton. (1642–1727)	133
12.	Hermann Boerhaave. (1668–1738)	135
13.	Edward Jenner (1749–1823)	145
14.	Réné Théophile Hyacinthe Laënnec. (1781–1826)	153
15.	Josef Skoda. (1805–1881)	156
16.	Carl Rokitansky. (1804–1878)	157
17.	Rudolph Virchow. (1821–1902)	160
18.	Oliver Wendell Holmes. (1809–1894)	168
19.	Charles Robert Darwin. (1809–1882)	170
20.	Louis Pasteur. (1822–1895)	176
21.	Lord Lister. (1827–1912)	187
22.	Robert Koch. (1843–1910)	190
23.	Paul Ehrlich. (1854–1915)	201



[From Traité des causes, des accidens, et de la cure de la peste. Paris, 1744.]

STALKERS OF PESTILENCE

Chapter I

PREHISTORIC MAN TO HIPPOCRATES

THE ANTIQUITY OF DISEASE

THE proven antiquity of disease makes it probable that illness has thrown its black shadow across human affairs ever since man emerged as man. And because man, even when most primitive tends to pour the chances and mischances that befall him into the mould of symbol, it is quite probable that, before the dawn of recorded history, certain rudimentary concepts of the nature of disease had found their way into his brain.

In this connection, a few references[1] to the scientifically proven evidence of the antiquity of disease may not be amiss. The origin and development of disease can be traced to some extent from the pathological lesions found on the fossil bones of ancient races of man and extinct animals, as well as by pathological researches on ancient Egyptian mummies. From the researches of Rudolf Virchow, the father of Paleopathology, Bernard Renault, Roy L. Moodie and others, it has been demonstrated that the history of disease properly begins with the early Paleozoic or Proterozoic, 100,000,000 or more years ago. The fossil remains of primitive vertebrates of the Paleozoic Era have yielded abundant evidences of such diseases as dental caries, pyorrhea alveolaris, osteomyelitis and fracture, diseases which apparently have changed but little, if at all, in the past 100 million years. As examples, may be mentioned the fact that caries has been found in the bones, scales and teeth of fishes from the Permian period in France; the mandible of a three-toed horse shows caries which resulted in absorption of the alveolar margins and exposure of the roots of the teeth, i.e. the sequence of events which may occur in pyorrhea alveolaris as we know it today; and caries of Pleistocene elephants has been noted. One of the most interesting facts of recent development is that arth-

ritis deformans, a disease found in so many Egyptian mummies, is identical with the "cave gout" (*Höhlengicht*) which Virchow,[2] in 1870, reported in bones of a Pleistocene cave bear, and which also is common in the skeletons found in the early German forests.

Regarding the existence of bacteria in prehistoric times, two methods of gaining knowledge of such ancient bacteria have been employed: (1) actual observation of bacilli, cocci or spores in thin sections of rock and (2) by inferring their presence from results which present-day knowledge has confirmed as due to bacterial action.

In 1914, Walcott[3] actually discovered bacteria in the oldest fossil-bearing rocks of North America, found in central Montana and dating back to the Cambrian and Pre-Cambrian periods, the very dawn of the geological history of animals. The bacteria discovered by Walcott were micrococci, occurring as single cocci and in short chains; their average diameter was from 0.95μ to 1.3μ. They were found in rocks in association with the earliest fossilized plants and animals, forms which flourished in the dawn of the world's history. Doubts that such delicate micro-organisms as bacteria are capable of preservation in a fossilized condition have been rather definitely disproved by other investigators, who have shown that fossil brains, fossil flowers, fossil blood cells,

muscle and kidney structures may be so well preserved that minute details of the tissues can be accurately seen.

Renault,[4] in 1895, as a result of twenty-four years of labor, found bacteria in the petrified feces or coprolites of fishes and reptiles, as well as in fragments of bone isolated from rock which dated back to geological ages succeeding the Devonian. He also observed bacteria in the stomach contents and in the teeth and jaws of fossil prehistoric vertebrates. It is well known that certain fishes have within their rectum a spiral valve which gives to the extruded feces an irregular ellipsoidal form, with characteristic markings. These coprolites Renault found at all levels of the Autun Lake, in France, especially in certain areas, as if the fishes had lived in swarms in this prehistoric Permian lake. Frequently in sectioning a coprolite one finds remains of bones, scales and morsels of food, the residue of digestion, which have contributed to the preservation of the coprolite. In fragments of bones and scales found in his coprolites, Renault discovered on sectioning the bones, that the lacunae and canaliculae often contained micrococci; whereas bacilli seemed to be more numerous in sections of scales than did micrococci. Renault named the micrococci M. lepidophagus, and described them as spherical cells ranging in diameter from 0.4μ to 3.2μ, with a tendency for

the cocci to appear in the diplococcus grouping and in short chains of four members. The bacilli Renault designated B. lepidophagus, and described them as cylindrical rods having a length of from 4.2μ to 5.2μ and a diameter of from 0.7μ to 1.0μ. According to Renault's description of the cocci and bacilli found in these ancient bony plates, one may surmise that the destruction of bone was performed in ancient times by micrococci and bacilli whose form and proportions approach in a most remarkable manner those bacteria which we describe today as the cause of caries of bone and teeth.

In the case of the earliest known example of osteomyelitis, in the fractured vertebral spine of a Permian reptile from Texas, bacteria of the micrococcus type were found by Moodie[5] in 1921 to be abundantly preserved in the distorted osseous lacunae. They were similiar in all respects to those found by Renault in the fossil bones of fishes.

PREHISTORIC MAN

The earliest prehistoric men probably had no formulated idea of the nature of disease. The hurts which they acquired during their pursuit of food, and in battles with their human and animal enemies, they probably accepted with the same unreasoning calm as they did the flicker of sunlight in front of their cave.

The "why of things" had not yet started its multitudinous echoes in his brain. But, in common with the lower animals with whom he contended for his existance, the instinct of preservation was strong within him, supplemented, as it always is, by a certain rude and primitive instinct for caring for his wounds, as well as by an instinctive hygiene. He shared with the wild beasts of the forests the instinctive hygienic lore which caused him to stretch and warm his body in the sunlight; when hurt he, too, hid in holes and caves; like the animal he, too, favored his foot when it was maimed. Like the animals he perhaps sought out certain herbs and grasses when he was sick. In this sense, the statement of Le Clerc[6] "the first man was the first physican" is true, because instinct teaches all beings possessing sensibility the rudiments of caring for their wounds. However, it would seem that these primitive, common-sense procedures more accurately represent the original rudiments of the art of nursing, which probably preceded the medical art, and was its initiative.

As the brain of primitive man developed, all sights and sounds in nature, the rustling of leaves, the flicker of sunlight, the flash of lightning, the crash of thunder, became visible signs and manifestations of spirits, malevolent gods, or demons. In short, he inextricably wrapped up the natural in supernatural trappings. There-

fore, he worshipped the sun, the wind, the lightning, the thunder—the era of simple nature worship. A further development in primitive man occurred when he first set up carved sticks and stones to represent these natural agencies, and thereby entered upon "fetish worship," and the practice of sacrifice to, and propitiation of, these symbols.

Primitive man, like the lowest grades of human life today, held originally to the concept that disease is an evil, extra-human spirit or the work of an evil spirit. Perhaps the next elaboration of the idea came when he began to look upon disease as the malevolent visitation of a human enemy possessing supernatural powers, whose spells and sorcery had to be met with similar weapons. And then, perhaps, as intimations of a spirit world outside the world of his daily affairs came to his awakening brain, disease began to be looked upon as the work of hostile or offended spirits of the dead.

From these primitive concepts of disease, the primitive "medicine man" and the "witch doctor" were perfectly natural and logical developments. They both assumed a solemn, and somewhat mysterious, supervisory relation to disease and its cure, not unlike that of the priest to religion. Quite generally, irrespective of geographical boundaries, the primitive "doctor" employed therapeutic pro-

cedures whose ultimate purpose was to "out-demon" the disease demons. Hence, he dressed in terrifying costumes and these, combined with his shaking of rattles and his ravings, both physical and vocal, were calculated to frighten the disease out of the patient in whom it had taken its residence. As a prophylactic procedure, charms and amulets were provided his patients, to ward off the demon's return in the future.

ANCIENT EGYPT

Although it is to ancient Egypt that we must look for the first beginnings of the art of medicine, as well as of philosophy, it is probable that the ancient Egyptian civilization, as well as that of Mesopotamia, was nearer to, and developed more closely from, the arts of prehistoric men of the Later Stone Age than has hitherto been believed. However, the earliest known physician of which history makes mention was an ancient and celebrated Egyptian of the third dynasty (4500 B.C.), known as Im-hotep,[7] "He Who Cometh in Peace." He was a physician of such repute that he was later worshipped at Memphis, and a temple was erected in his honor upon the island of Philae.

In ancient Egypt, at first the priest and the physician were identical, and medicine never became fully dissociated from religion. Disease and death were believed to be

not natural and inevitable, but to be caused by some malign influence which could use any agency, natural or invisible:

Often it belongs to the invisible world, and only reveals itself by the malignity of its attacks; it is a god, a spirit, the soul of a dead man, that has cunningly entered a living person, or that throws itself upon him with irresistible violence. Once in possession of the body, the evil influence breaks the bones, sucks out the marrow, drinks the blood, gnaws the intestines and the heart, and devours the flesh. The invalid perishes according to the progress of this destructive work; and death speedily ensues, unless the evil genius can be driven out of it before it has committed irreparable damage. Whoever treats a sick person has, therefore, two equally important duties to perform. He must first discover the nature of the spirit in possession, and if necessary, its name, and then attack it, drive it out, or even destroy it. He can only succeed by powerful magic, so he must be an expert in reciting incantations, and skillful in making amulets. (Maspero[8]).

Incantations, with their implied or apparent magic element, were looked upon by the ancient Egyptians as of very great importance. Those ancient men fell prey to the same diseases as they do today. Sir Marc Armand Ruffer,[9] in a series of papers dating from 1909 to 1920, described Pott's disease in an Egyptian mummy dating from about 1000 B.C.; he gave a

detailed note on an eruption resembling that of smallpox in the skin of an Egyptian mummy of the twentieth dynasty (1200–1100 B.C.); he discovered from examinations of mummies that arthritis deformans and spondylitis occurred in ancient Egypt, and he discovered the presence of "Bilharzia hematobia," an animal parasite, in Egyptian mummies dating back to 1250–1000 B.C. The voice of the white-robed Egyptian priest comes with a pathetically reminiscent ring across the centuries as he lifted his brown arms to the sky and chanted the magical formula: "O demon who art within the abdomen of So-and-So, son of So-and-So, O Thou whose father is surnamed He who causes heads to fall, whose name is death, whose name is the male of death, whose name is accursed to Eternity."[10]

The amulet is the oldest form of prophylaxis against disease.[11] Originally, organs such as the brain, testicles and marrow of animals were devoured, for the purpose of reinforcing an individual's functions and his natural resisting powers. From this original concept was derived the simpler custom of wearing on the body portions of animals, or insects such as spiders, which were believed to be immune to poisons. Even rare and odoriferous objects were worn.

Although the ancient Egyptians held to the "spirit" or "god" origin of disease,

and although magic, spells, incantations and prayers held a major part in their therapeusis, yet records going back thousands of years establish the fact that the early Egyptians employed emetics, purgatives, enemata, diuretics, diaphoretics and even bleeding as adjuvants to their psychotherapy. Later, specialism developed to such an extent that Herodotus (ii, 84) made a most modern sounding observation when he wrote that "the country is full of physicians; one treats only the diseases of the eye; another those of the head, the teeth, the abdomen, or the internal organs."

In another connection, Diodorus Siculus remarks that so evenly ordered was the whole manner of life of the ancient Egyptians that it was as if arranged by a learned physician rather than a law-maker. Cleanliness of the person, of houses, and of cities was strictly regulated by law. The priests, by their frequent ablutions and their spotless clothing, did much, by force of example, to stimulate interest in personal hygiene among the people.

Moreover, according to both Diodorus and Herodotus the ancient Egyptian's belief that most diseases came from overeating led to the custom of employing, for three consecutive days in each month, emetics and enemata for prophylactic reasons. It is of interest to note that the word "chemistry" is said to be derived from "Chemi" (the "Black Land"), the ancient

name of Egypt, whence the science was called The "Black Art."[12]

The ancient Egyptians credited their Gods with having maladies similar to those of men. Rē had sudden diseases of the eye (thought to be symbolic of eclipses); and Horus not alone had headaches and internal pains, but he had dysentery and anal weakness as well.[13] (Jayne).

Worm diseases were recognized by the ancient Egyptians, a rather remarkable feat in view of the fact that even today painstaking, and often microscopic, examination is frequently necessary to establish a diagnosis. The Egyptian anemia, variously considered to be hookworm disease or bilharziosis,[14] was thought by the ancient Egyptians to be sent by Ā Ā Ā, the God of Death and, according to the Ebers Papyrus, which dates back to about 1550 B.C., its immediate cause was ascribed to the worm Neltu.

According to Klebs,[15] Herodotus gives an account of regulated inspection of the meat destined for sacrifices. He states that the priest or inspector was on the lookout for such relatively small parasitic invaders as the Cysticercus, and that in instances where only parts of the animal were sacrificed, the remainder was available for consumption after a sanitary inspection had been made.

BABYLONIA AND ASSYRIA

The ancient Babylonians and Assyrians also attributed a supernatural origin to

disease, believing it was caused by the presence in the body of spirits, ghosts or demons. Again it might be due to the "evil eye," or to the attack of a human enemy operating through a wizard or witch or other practitioner of black magic, or even through the agency of an offended deity. Cure of disease, therefore, depended upon the dislodgement and expulsion of the evil being by some higher, divine power; hence the treatment of disease was a matter of religion and was under the direction of the priests, who for the most part acted as physicians.[16] Their not infrequent practice of administering to the patient foul and ill-smelling substances such as dung and urine, was apparently in order to disgust the invading demon of disease, and make his residence within the body so disagreeable that he would depart.[17]

The Babylonians had a large number of healing gods, to whom they sacrificed, and both the ancient Babylonians and Assyrians gave names to the individual demons of disease. Ashakku was the demon of wasting diseases; Namtar the demon of plague; Alu a demon that clouds one's vision. Jastrow[18] says:

> The Babylonians and Assyrians thus recognized an entire faculty of demons. The age of specialization had set in which assigned a special function to each demon, although the professional ethics of demonology did not bar

the demons from encroaching on the domain of a colleague.

Klebs,[15] commenting on the fact that primitive peoples unschooled in modern scientific methods of experiment often give evidences of minute and accurate observation, mentions that on various ancient Assyrian monuments divinities are depicted in the act of manually fertilizing the flower of the date palm. Continuing, he says:

Theurgic and numinal concepts form the basis of the nosological nomenclature of the ancient Babylonians. The study of cuneiform inscriptions has opened our eyes to a new world. The texts which deal with incantations, divinations, conjurations (exorcisms) and the like contain a great deal of information on medical subjects. The priest, who filled the place of the physician, as so often in history, used these texts as a sort of practical guide-book in his daily routine. They were to lead him to diagnosis, prognosis, prophylaxis and treatment of human ills. The compilation of the most important ones can be traced to the non-semitic priests and magicians who practiced their craft before the advent of the semitic Babylonians (dated variously between 5000 and 4000 B.C. or, roughly, before 3000 B.C.).

Montaigne, in referring to the ancient Babylonians, says: "the whole people was the physician." This remark is probably explained by the quotation from Herodotus (1:80):

They bring out their sick to the market place, for they have no physicians; then those

who pass by the sick person confer with him about the disease, to discover whether they have themselves been afflicted with the same disease as the sick person, or have seen others so afflicted; thus the passers-by confer with him, and advise him to have recourse to the same treatment as that by which they escaped a similar disease, or as they have known to cure others. And they are not allowed to pass by a sick person in silence, without inquiring into the nature of his distemper.

According to the Code Hammurabi[19] (2250 B.C.) a physician's fees in ancient Babylonia were strictly regulated by law. Ten shekels was the statutory fee for treating a wound or opening an abscess of the eye. If the doctor caused the patient to lose his life, or his organ of vision, the law prescribed that the physician's hands be cut off. Sudhoff,[20] in 1911, first developed the fact that the Assyro-Babylonians were the first ancient people to recognize the transmissibility of leprosy. He says that all lepers were outlawed from the community and the formula of outlawry, carven upon the stone landmarks of Babylon more than 3500 years ago, read: "Nevermore shall he know the ways of his abiding place."

PAGAN SEMITES

Very little is known regarding the views of disease held by the Phoenicians and other pagan west-Semites, but theurgy, or magic, was apparently the basis of their methods of healing.[21]

ANCIENT INDIA

In the earliest Sanskrit documents, the Rig Veda (1500 B.C.) and the Atharva Veda,[22] we find that the Aryans of ancient India regarded disease as the manifestation of the power of some supernatural being, not infrequently arising from the gods in punishment for sin, or sometimes due to the mere caprice of a malevolent or capricious deity. Treatment, therefore, was largely a matter of spells and incantations, hymns and sacrifices. Because the gods were often vague and uncertain, the people attributed great power to magic and sorcery in compelling the gods to obey the will of man. In ancient Hindu writings are found frequent references to the demons of disease.

They are generally vague in outline and indefinite in number, and are known as *raksas* (injurer), *atrin* (eater) . . . and the like. Takman (fever), a demon, "king of diseases," was flatteringly implored to leave the body and was threatened with annihilation if he should not choose to do so. Sitala (the "Cool Lady," with an euphemistic allusion to the burning fever) was smallpox; mania a possession by *bhutas*, or ghosts; and epilepsy was the result of possession by dog-demons.[23]

In the Brahmanical period (800 B.C.–1000 A.D.) medicine was in the hands of the Brahman priests and scholars.

Hindu physiology presupposed that the vital processes are actuated by means of the air

(below the navel); the bile (between the navel and the heart), and the phlegm (above the heart); from which are derived the seven proximal principles, chyle, blood, flesh, fat, bone, marrow and semen. Health consists in a normal quantitative relationship of these primary constituents, disease in a derangement of their proper proportions.[24]

Susruta, the famous Brahman physician of the fifth century A.D., gave a very recognizable description of malaria, *and attributed the disease to mosquitoes.* After the Mohammedan conquest, Hindu medicine virtually ceased to exist. The great contribution of the ancient Hindus was the remarkable skill they developed in operative surgery.

ANCIENT IRAN

In the Iranian religion, reformed by Zoroaster, disease was looked upon as a diabolical entity, and was often named after the particular demon causing it. Sin and disease were on much the same plane; sin being a spiritual, and disease a bodily malady, a breach of the moral or physical order resulting from pollution, visible or invisible. This pollution must be removed by some rite of purification; hence invocations, hymns and magic must accompany the administration of natural remedies. Like the Babylonians, the Iranians worshipped, and sacrificed to, a considerable number of healing gods.

ANCIENT HEBREW MEDICINE

The Bible and the Talmud are the principal sources of our knowledge of early Hebrew medicine. In the old Testament, disease is listed as an expression of the wrath of God, and cure is to be effected by moral reform, prayers and sacrifice. In Exodus (15:26) God says: "I will put none of these diseases upon thee, which I have brought upon the Egyptians; for I am the Lord that healeth thee." Physicians were a distinct class, however, apart from the priests, and professional midwives are mentioned in Exodus. The only surgical procedure mentioned in the Bible is found in the second book of Exodus (4:25) where Zipporah, the wife of Moses, "took a sharp stone and cut off the foreskin of her son."

Klebs[15] points out the fact that the *correlation between mice and bubonic plague was recognized in Biblical times*, as recorded in II Samuel (2:3). After the Ark of the Covenant was captured by the Philistines and taken to Ashdod, a plague of emerods (hemorrhoids, or tumors, usually identified with bubonic plague) broke out in the town. After the plague had spread along the coast, the priests and diviners advised that the Ark be returned to the Israelites, with a trespass offering, consisting of five golden emerods and five golden mice "according to the numbers of the lords of the Philistines," to represent "images

of your emerods and images of your mice that mar the land . . . to lighten his hand from off you, and from off your Gods, and from off your land." (II Samuel 6:5.)

Klebs further states: "The concepts of the insect pests among the Biblical people are largely derived from the Babylonians. Thus the fly, the mosquito and other diptera play also with them a rôle in cult and elsewhere. Ekron held an ancient and famous shrine dedicated to Baal-Zebub which name, literally translated, means the "Lord of Flies."

The Talmud, although essentially a law book dating from the second century A.D., contains some rather detailed information concerning Jewish medicine. In the Talmud is displayed considerable knowledge of anatomy, as well as of surgery, probably derived in part from the fact that the ancient Hebrew religion held that the meat of diseased or injured animals was unfit food. The autopsies performed upon slaughtered animals led to some knowledge not alone of comparative anatomy, but of comparative pathology as well, and it is interesting to note that the ancient Hebrews were acquainted with caseous degeneration and tumors of the lungs, as well as with atrophy and abscess of the kidney, and cirrhosis and necrosis of the liver.

The sanitary code of the Jewish people, contained in the Old Testament, is one

of the epochal contributions to sanitary legislation, and the science of social hygiene may be said to date from it.

ANCIENT GREECE

Before Hippocrates. In the Iliad and the Odyssey of Homer, it is made evident that in the early period the Greeks looked upon disease and death as punishments inflicted on mankind by angry or vengeful gods. In the Odyssey (11:411–412) Homer says: "It is by no means possible to avoid disease sent from Zeus; yet do thou at least pray to thy father, even unto King Poseidon." Religion in ancient Greece was an affair of rituals, not beliefs, and sacrifice was the recognized expression of piety from early times. The ancient Greeks held an intimate and friendly attitude toward their gods, and their religion and worship of the celestial deities was joyous and bright. Herakleitos said: "Men are mortal gods, and gods are immortal men." In one phase, however, their religion was dark and gloomy, namely in their worship of the black and hidden divinities of the Earth and Underworld. "These divinities ranged from Hades, the great death-god, and his consort, the dread Persephone, rulers of the Underworld realm, to demons, demigods, heroes and the vast horde of the spirits of the dead."[25]

As has been said, disease and death were looked upon by the ancient Greeks as

caused by superhuman agencies of the Celestial World, of the Earth or of the Underworld. Disease was thought to be sent by Zeus, yet in the Odyssey (1:30) Zeus says to the immortals: "Alas! How, for sooth, do mortals reproach the gods! For they say that their evils are from us; whereas they themselves, through their own infatuation, suffer griefs beyond what is destined." In the Iliad (1:50) Apollo sends diseases and death among men; and Artemis inflicts disease, particularly mental and nervous disorders, and death among women. In the Hippocratic treatise, "De Morbo Sacro" (The Sacred Disease) it is written: "But terrors which happen during the night, and fevers, and delirium, and jumpings out of bed, and frightful apparitions, and fleeing away—all these they hold to be the plots of Hekate, and the invasions of the Heroes."[26] And in the same treatise, it is said of epileptics that

> If they imitate a goat, or grind their teeth, or if their right side be convulsed, they say that the mother of the gods (Cybele) is the cause. If they speak in a sharper, shriller tone, they liken this state to a horse and say that Poseidon (Neptune) is the cause . . . but if foam be emitted by the mouth and the patient kick with his feet, Ares (Mars) gets the blame.

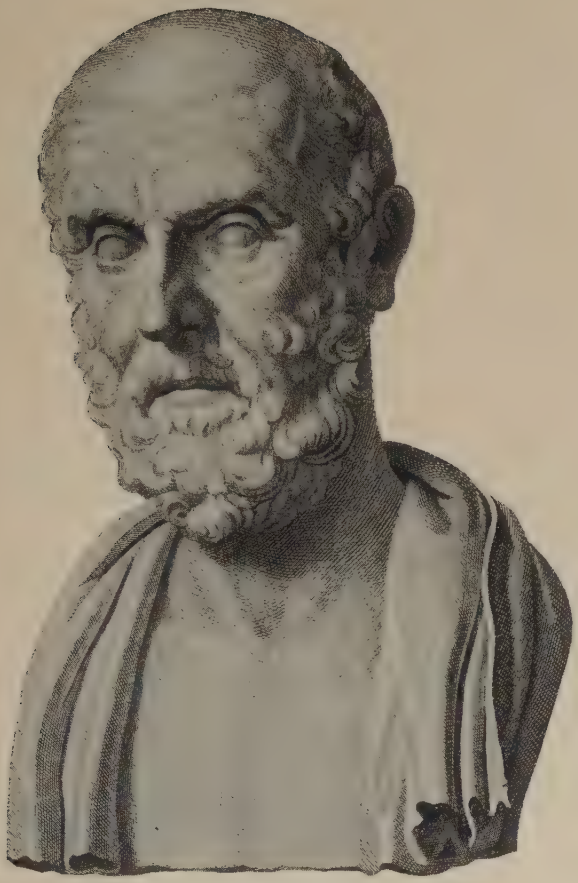
Sudden illness was ascribed to Pan (Euripides, Medea, 1170 t.f.). Contagion as the cause of the spread of disease was not recognized by the ancient Greeks.

Before the time of Hippocrates, Greek medicine was regarded merely as a branch of philosophy.

THE CLASSIC PERIOD (AGE OF HIPPOCRATES)

Now, out of the shadows of those ancient days, emerges the even more shadowy figure of Hippocrates (460–370 B.C.). On the stage he trod, such contemporaries of his as Plato and Aristotle emerge as distinct, clearly-limned individuals; on their lives history has thrown definite highlights and shadows. Hippocrates, on the other hand, is almost completely a figure of shadows. There is no doubt that Hippocrates actually lived, but the details of his existence are meager. He was mentioned only twice by Plato and once by Aristotle, and that is about all that is known of him from contemporary sources. The meager, and often disputed, details of his life were supplied by the Greek physician, Soranus, who wrote his Life of Hippocrates five hundred years after the death of Hippocrates.

According to Soranus, Hippocrates was born in Cos, and tradition records that he was either nineteenth or seventeenth in direct descent from Aesculapius. He is said to have studied medicine under Heraclides, his father, and Herodicus of Selymbria, and philosophy under Democritus of Abdera, the originator of the doctrine of



Hippocrates.
(460–370 B.C.)

atoms. He is said to have taught and practiced medicine in Athens, as well as probably in Thrace, Thessaly, Delos and Cos. He died at Larissa, in Thessaly, at an age variously estimated at from eighty-five to one hundred and nine years.

Paralleling the historical tenuity of Hippocrates' life, there is a corresponding lack of agreement in regard to the exact share he had in the authorship of the medical works which bear his name. Doubt has even been expressed as to whether the Hippocratic Oath, which for over two thousand years has voiced the highest aspirations of the medical profession, should be attributed to him. Certain of the treatises are generally considered to be genuinely Hippocratic, but about others there is more or less substantiated doubt. Even in respect to the admittedly genuine Hippocratic writings, there can be little but conjecture as to exactly how great a part Hippocrates played in their actual authorship. Perhaps he was the sole author. Much more probably he was an editor of a series of writings that represented the most advanced medical thought of his day, to which he added the precious increment which genius alone can bring. If this latter alternative be the correct one, Hippocrates well might answer as did Charles Reade, when he was accused of plagiarism: "I have milked 300 cows, but the cheese thereof is mine!"

Hippocrates, nebulous though he be, represents so definite a landmark in the history of Medicine, that it is advisable briefly to recapitulate the ideas concerning disease held from prehistoric times up to the beginnings of the Classic Period. When this is done, we are forcibly impressed by the uniformity of concept held by diverse races and peoples during this long period of time. Minor variations and elaborations there were, it is true, but the basic thread of thought running through the minds of these ancient men was that disease represented the visitation into the body of malignant spirits or gods. The element of the supernatural, of magic, was so dominant that thought and accurate observation were largely inhibited, and treatment was intrinsically a matter of ritual.

To Hippocrates belongs the peculiar distinction that he was the first definitely to discard the idea that disease was due to the gods or other fantastic imaginings; he dissociated medicine for the first time from religion and philosophy. This alone would have been sufficient to insure his immortality, but he went further, and by crystallizing the loose knowledge of his predecessors and contemporaries into systematic science, he became the master to whom modern medicine owes the art of clinical inspection and observation. So keen were Hippocrates' powers of observation, and so clear are the written descrip-

tions ascribed to him of such diseases as tuberculosis, puerperal (child-birth) convulsions, and epilepsy that, with a few changes and additions, they might be incorporated entire in any modern textbook of medicine. And who, incidentally, has ever enriched man's intellectual life with a finer aphorism than the following, which is found in "The Aphorisms"[27]: "Life is short and Art is long; the Occasion fleeting, Experience fallacious, and Judgement difficult?"

A South Italian physician, Empedocles (504–443 B.C.) of Agrigentum, Sicily, laid the foundation upon which was elaborated the Hippocratic theory of disease. He it was who introduced into philosophy the theory that all bodies are built up, in varying proportions, of the four-fold elements earth, air, fire and water. Upon the proper equilibrium of these four basic elements health depends; disease results from a disturbance of their balance. Empedocles also enunciated the theory of the conservation of energy; he taught that all things are flowing and are capable of transformation, but that nothing can be created and nothing can be destroyed.

The broad basis of reasoning upon which the Hippocratic system of medicine is built should be considered before a closer analysis of his views concerning the nature of disease is attempted. Although he was reputed to be a member of the family of

the Asclepiadae, priest-physicians steeped in traditions of magic and priestcraft, the bed-rock of his contention was that medicine must be dissociated from priestcraft and philosophy. In the "de Aere," (29) it is expressly stated that attention should exclusively be directed to the natural history of disease and that diseases must be scientifically treated as subject to natural laws. Charms, amulets, incantations were anathema to him, trappings of an outworn magic which had no place in medicine. In speaking of epilepsy, which had long been looked upon as a sacred disease, Hippocrates wrote: "It appears to me to be no wise more divine nor more sacred than other diseases, but has a natural cause from which it originates like other affections; men regard its nature and cause as divine from ignorance." Here is enunciated the "Magna Charta" of medicine, and to Hippocrates can rightfully be given the title of the "Emancipator of Medicine" from superstition. It is no proper reflection upon his genius that some of his medical descendants, ancient as well as modern, attempted to rewed medicine and magic.

Hippocrates, intellectual giant that he was, was handicapped by certain definite limitations of knowledge. The sacred veneration which the ancient Greeks felt for a dead body precluded dissections, and hence the knowledge of anatomy,

physiology and pathology possessed by Hippocrates was incomplete and confused. He seemed to have no conception of the infectiousness of epidemic diseases, as we know it today, and he attached a quite erroneous importance to "miasmas" as a cause of disease. The book entitled "On Winds" states: "According to all appearance the cause of disease should be found in the air, when it enters the body in excess, or in insufficient quantity, or too much at a time or when tainted by morbid miasmas." In the book on "Humors" we find: "Diseases develop from odours exhaled from mire and marshes," and in the "On the Nature of Man" it is stated that the cause of epidemic diseases resides "in the air from which escapes a morbid exhalation contained within it" and the air is listed as the only possible "universally acting cause" of wide spread disease. And yet Hippocrates seemed to have rather definite ideas regarding infection from water, for we find that not alone did he advise that water be boiled before it was drunk, but we find in the famous treatise "On Airs, Waters and Places":

> The still and stagnant waters of marshes are the cause of diarrhea, dysentery and intermittent fever (malaria). Those cities which are favorably placed for the sun and the winds, and where the waters are of good quality, are less touched by these disadvantages. But those where stagnant and marshy

waters are used, and whose site is bad, suffer more from them.

It is interesting to note, as pointed out by Singer[28] that Thucydides (B.C. 471–391), a contemporary of Hippocrates, was the first writer to whom can be traced a definite and formal belief in the passage of specific infectious disease from one person to another. In his "History of the Pelopennesian War," (11:47 ff.) he said, in speaking of the plague of Athens, that those who came most intimately in contact with the sick were the most liable to contract the disease. Thus among the ancient Greeks, as well as the ancient Romans, although the widespread nature of epidemics was largely a mystery, yet the effects of excessive rainfall, certain winds, the seasons, overcrowding and the inhalation of air breathed by others, as well as unburied corpses, were all considered dangerous to health. However, with the ancients, it was miasma rather than contagion that was most feared.

Although the central idea of Hippocrates' humoral pathology in regard to the causation of disease has largely been discarded, yet it marked a distinct advance over concepts hitherto held by its insistence that disease resulted from a derangement of certain fluids of the body, brought about by natural laws that are subject to no magical influence. The monumental advance made by Hippocrates in his concepts of

disease becomes the more graphic when one realizes that the very essence of his teaching was the existence of a formative, conservative and curative power in the human body, by which it preserves itself and combats morbid causes of disease, and the effects produced by them. Its scientific virtue lay in centralizing attention upon bodily changes, a virtue not vitiated by numerous errors of detail which are incorporated in Hippocrates' theory. It postulated that, corresponding to the four elements (fire, air, water and earth) and the four qualitites (hot, cold, moist and dry) there are four humors or fluids of the body, viz. blood, phlegm, yellow bile and black bile. Health was considered to depend upon a proper balance of these humors, and disease upon an imbalance. Hippocrates taught that such general causes of disease as heredity, climate, the seasons, and the epidemical constitution acted by disturbing the equilibrium of the body, specifically by changing the humors. For example, fever resulted from a heating of the bile or from an increased production of phlegm which caused the tissues to swell, thereby interfering with the secretions; a chill was considered to be an indication that phlegm had become mixed with the blood. The fermentation or putrefaction of the humors, from which fever and contagion were believed by the Hippocratic School to arise, might manifest itself exter-

nally, as in various skin diseases and in septic sore throats, or it might be confined to the internal structures of the body, and not become visible.

The tremendous influence which Hippocrates exerted upon medical thought is amply attested by the fact that his doctrine of disease survived, with minor modifications, for almost twenty-two centuries. The masterful clinical grasp of Hippocrates, largely made possible by his powers of minute observation and analysis, is abundantly testified in his writings. In his book on "The Uses of Liquids" he observes that when fishermen suffer wounds, suppuration does not tend to occur, unless the wounds are meddled with; and he extols the anti-putrefactive properties of sea-water. Infectious processes following wounds, such as pyemia, erysipelas and tetanus were accurately described by Hippocrates, as well as infections following labor and miscarriage. In "Diseases of Women" we read:

> If the womb is ulcerated, blood, pus and icherous fluid are discharged . . . the belly becomes distended . . . and it is painful to touch as is a wound. Fever, grinding of the teeth, continued pain in the genital parts, pubis, lower abdomen, flanks and lumbar region ensue; this disease is especially prone to occur after a labour when something putrefies in the womb; it also occurs after abortion.

In the books of the "Epidemics," is detailed a case of a wound of the skull

with splinters of bone which required trephining. It tells how pus formed and how, on the eighth day, a chill occurred, followed by fever. It points out that the fever and chills are due to the accumulation of pus and it recommends a thorough cleaning out of the wound by a surgeon as the only means of saving the patient's life. In the same book reference is made to a case of abdominal suppuration in which cauterization stopped the discharge of pus, but because of a mistake in diet during very warm weather fever and diarrhea developed, and the patient died. It is interesting to observe that Hippocrates not only resorted to heat for destroying the focus of pus, but he attached great importance to the patient's resistance, and comments on the fact that the good effects from his operative procedure were vitiated by the patient's indiscretion in the matter of diet. Hippocrates also recognized the connection between pus and fever, because we find: "The majority of patients who have suppurative processes are seized with chills and fever."

Aristotle (384–322 B.C.). Hippocrates, contemporary as he was of Socrates, Plato, Sophocles, Herodotus and Euripides, was one of a most distinguished coterie that helped to make his period the time of the greatest flowering of the Athenian Republic. And yet, fourteen years before the death of Hippocrates, there was born in

Stagira, in Macedonia, the master of them all, Aristotle. Within the short span of his sixty-two years of life, he became the creator, the shaper, and finally the ruler of an intellectual empire greater than any single other human mind has ever compassed. Father of the sciences of physiology, comparative anatomy, botany, and systemmatic zoology, he was indisputedly the greatest figure in natural history and biology for over two thousand years. But natural history constituted but one field of his intellectual domain; he was equally master in the spheres of ethics, poetry, psychology, government, rhetoric, logic, and metaphysics. Parenthetically, it is interesting to note that, according to Strabo, Aristotle was the first book collector of whom we know, and he is said to have taught the kings in Egypt the arrangement of a library.

Aristotle is not in the direct line of those who specifically helped to shape man's ideas in regard to the nature of disease, but his biological contributions, as well as his insistence upon the necessity of knowledge of natural science, were of fundamental import in the development of the art of Medicine. He was the first to study, day by day, the embryological development of the chick; he observed the fetal heart beat, the enveloping membrane, and the vitelline and allantoic veins. He it was who named the aorta, but he did not

differentiate between arteries and veins. The heart he wrongfully considered to be the source of the blood, the source of innate heat, and the seat of sensation and thought; the pulsation of the heart and blood vessels he believed to be due to a bubbling of the blood caused by the action of the vital heat. The blood, he taught, was cooled by the pneuma, or spiritus, drawn in by the lungs. Moreover, Aristotle denied that the brain feels and thinks, and he contended that the brain is a gland whose function it is to secrete cold humours, which prevent an over-heating of the body by the fiery heart.

After the death of Hippocrates, his son-in-law Polybus carried on the torch of medicine which he had lighted, as did Dioxippus of Cos and Petronius and Diocles, the latter being called by the Athenians "the second Hippocrates." The School of Alexandria, resulting from the colonization of Greek medicine in Egypt, is particularly notable for its anatomical discoveries which so profoundly influenced ancient medicine. Of this school, the most famous leaders were Herophilus and Erasistratus (300–225 B.C.), the famous anatomists who are said to have originated dissecting. The activities of the Alexandrian School were concerned with more or less minor modifications of Hippocrates' methods of treatment.

THE GRAECO-ROMAN PERIOD

(146 B.C.–476 A.D.)

Before Galen. Paraphrasing Carlyle and Emerson we might say: "Beware when God lets loose a thinker on the world, for all things then have to rearrange themselves." An Hippocrates has some such action in changing the latent but unorganized possession of facts to definite conscious possession of truth as does a crystal added to a supersaturated solution. Not alone that, but a ferment is set in other men's minds, a catalyzer of the intellect that activates otherwise latent and slumbering thought processes. Before Hippocrates, the supernatural trappings with which disease had been invested had served to inhibit men's imaginings in regard to the nature of disease. After Hippocrates, the floodgates of theorizing opened. Following his lead, attention became centralized upon bodily alterations as constituting the essence of morbid processes, but theory unsupported by experimental facts led medicine during the major part of the Graeco-Roman period into cul-de-sacs of sterile dialectic.

Thus we find Asclepiades, born in 124 B.C., advancing an "atomic" or "corpuscular" theory of disease, based on the teachings of Epicurus. He taught that the human body, like other matter, is composed of small, unchangeable and individual atoms, the soul also consisting

of atoms in a more subtle state. Illustrative of the ingenious, but misguided lengths to which he went is the following quotation from Cumston:[29]

Asclepiades states that the human body remains in its natural state as long as matter is freely absorbed between the pores, the interatomic spaces, so that health results from a correct proportion of pores in relation to the matter which they should absorb and allow to pass. Death is a result of a disproportion between the pores and matter. The most common accident is obstruction of these pores, which, according to Asclepiades, produces phrensy, lethargy, pleurisy, high fever and pain. If the pores are too oblique, the result will be the production of fainting, languor, exhaustion and so forth, while extreme emaciation and hydropsy are the result of extreme dilatation of the pores. Hunger is engendered by opening of the large pores of the stomach and abdomen, while thirst is due to opening of the smaller ones. Finally, from a rather obscure passage in Caelius Aurelianus, it would appear that Asclepiades admitted a third cause of disease, namely, a disturbance or confusion of the body juices, or the mixture of liquid matter with the spirits. He explained intermittent fever (malaria) as follows: The quotidian is produced by the retention of the largest of all the atoms, the tertian by that of the medium atoms, and the quartan by that of the smallest.

Asclepiades discarded the idea that there are any specific remedies for the various organs of the body, and he ridiculed the

passiveness of the Hippocratic School, saying: "the practice of the ancient physicians was merely a meditation on death." The so-called Empiric School of Medicine, of which he was the leader, has gone into the limbo of historical curiosities, but Asclepiades remains of interest because of the fact that he was the first to mention tracheotomy.

The main contribution of Themison (123-43 B.C.) who practiced medicine in Rome during the reign of Augustus, was his division of diseases into two classes, the acute and the chronic. Founder of the so-called Methodic School, he modified the "pore" theory of Asclepiades by teaching that the principal causes of disease were (1) a constriction (*strictum*) of the pores of the body, (2) a relaxation (*laxum*) of the pores, and (3) a mixed cause, resulting from a constriction of the pores in one part of the body and a relaxation of the pores in other parts. Themison followed Hippocrates in distinguishing three periods in the evolution of disease: (1) a period of increase, (2) a period of full development, and (3) a period of decline.

Thessalus (A.D. 60), who also practiced in Rome, introduced a still further modification of the "pore" theory. Whereas Themison and Asclepiades had taught that health resulted from a symmetry of proportion of the pores, and disease from a disproportion, Thessalus believed

that in order to cure a disease the condition of the pores in the diseased part should be entirely changed, and from this theory is derived the word "metasyncrisis," which signifies a change in the pores. Mustard was a favorite metasyncritic drug employed by Thessalus. Not content with damning Hippocrates by characterizing his "Aphorisms" as a tissue of lies, and with stating that all physicians who had lived before him had done nothing useful, Thessalus made a pathetically ridiculous gesture to posterity by ordering that upon his tomb should be engraved the words: "The Conqueror of Physicians."

Methodism, founded by Themison, continued to be the most important of medical sects during the second century A.D., at least in Rome, and during this century its two most distinguished champions were Soranus of Ephesus, the greatest gynecologist of antiquity, and Caelius Aurelianus, a contemporary of Galen. Both Soranus and Caelius held strongly to the pore constriction and pore relaxation idea of the causation of disease, and they divided the principal types of acute diseases into three main categories: (1) phrensy (ataxic fever) and lethargy (adynamic fever) result from a constriction of the pores; (2) cardiac disease is due to relaxation of the pores, and (3) pneumonia and pleurisy are in the mixed type, i.e. these diseases result from a constriction of

the pores in certain parts of the body and a relaxation of the pores in other parts. Among chronic diseases, vertigo, asthma, epilepsy, melancholia, jaundice, paralysis, catarrhs, phthisis, colics and dysentery are due to constriction of the pores (Caelius); diarrhea and hemorrhagic and menstrual flux, when excessive, are due to relaxation of the pores; whereas hydropsy belongs to the mixed type.[30] Caelius was an ardent champion of the belief that no such thing as a local disease exists; he contended that when a person is ill, the entire body is diseased, an opinion that is considered today the ultramodern conception of such a disease as pneumonia, which is looked upon as a disease of the entire body, with marked localization in the lung. From this, Soranus held the extreme opinion that the search for the organ principally diseased is a bootless task, and both Soranus and Caelius denied that there were any specific drugs, i.e. drugs having a particular action on a given organ.

During the second century A.D. Aretaeus the Cappadocian extended the theory of infection advanced by Thucydides. In his volume on "The Causes and Symptoms of Acute Diseases," he distinguished definitely between contact infection and infection at a distance.

Galen and the Restoration of Hippocratic Medicine. Medical thought during the Graeco-Roman period was characterized

by rebellion against the teachings of Hippocrates and a grotesque theorizing upon the nature of disease, unsupported by a sufficient body of facts. The advent of Galen marked a return to Hippocratic medicine.

Galen, whose full name was Claudius Galenus, flourished from 130 to 200 A.D. After studying medicine in Greece and Egypt, he came to Rome to practice when scarcely thirty years of age. He was contemptuous of the various sects, such as the Methodists, Empirics, etc. and he accepted the teachings and precepts of only one master, Hippocrates. Equipped with an extremely active mind whose tendency was always to explain facts by hypotheses, and possessing an encylopedic knowledge of medicine, Galen did not so much advance man's knowledge of the nature of disease as to refurbish the Hippocratic doctrines in more popular and attractive trappings. This statement would seem to hold true in spite of the fact that Galen was not alone the supreme anatomist up to the time of Leonardo Da Vinci (1510) and Vesalius (1543), but certain of his discoveries would seem to entitle him to consideration as the first great experimental clinician. It is most intriguing to observe how closely Galen came to the discovery of the circulation of the blood. He demonstrated that the arteries contain blood, and brought out the fact that the blood pulsates

Galen.
(130–200)

between the heart and a ligated artery, where it is stopped. He demonstrated the difference between the motor and the sensory nerves, and even distinguished the motor and sensory roots leaving the spinal cord; he also recognized the difference between intercostal and diaphragmatic breathing.

Like Hippocrates, Galen recognized four elements (fire, water, earth and air) and their four qualities (heat, moisture, cold and dryness) as constituting the basis of all parts of the body. He taught that the body consists of three distinct parts: (1) the solid parts, such as bones, ligaments various organs, etc., which he likened to containers; (2) the liquid parts or contents, such as the blood, lymph and bile; and (3) spirits, or forces. These latter "spirits" he believed to be three in number (a) natural spirits, which were a subtle vapor arising from the blood (which, itself, was formed in the liver); (b) vital spirits, which were formed by natural spirits going to the heart and there combining with air; and (c) animal spirits, which resulted from the transformation of vital spirits in the brain. (Parenthetically, it is to Galen that the doctrine of Vitalism, still debated in physiology and biology, is to be traced.)

Galen, moreover, admitted four principal body humors: (1) the blood, a hot and moist humor, (2) pituit, or lymph, a cold and moist humor, (3) yellow bile, a hot

and dry humor, and (4) black bile, a cold and dry humor. Most diseases, he held, arose from an excess, or deficiency, or an alteration in these four fundamental humors and their specific qualities. Perfect health, on the other hand, occurs only when complete equilibrium exists between the four humors and their four qualities.

It was from these concepts that Galen built up his classification of temperaments, which he subdivided into four primary types: (1) the sanguine, (2) the phleg matic, (3) the bilious and (4) the melancholic. Each of these temperaments he believed to be either hot, or cold, or moist or dry. Differences between temperaments, and their divergence from the normal, he looked upon as predisposing causes of disease; the exciting causes being a disordering of the humoral equilibrium. Hence, each disease demands its particular curative treatment; in one disease the humors must be thinned; in another thickened; in one cooled, in another warmed; in one purified, and in another evacuated. Galen was an ardent advocate of bloodletting, but he said it was better to err on the side of insufficient bloodletting than of excess. Galen's idea that "coction" or suppuration is an essential part of the healing of a wound gave rise to the theory of "laudable pus," an error which was not completely dispelled until the researches of Lister and Pasteur, in the latter half of the past century.

Galen followed the Hippocratic school in attributing the cause of epidemics to atmospheric conditions; he emphasized the effect of climate, as well as the degradation of the air, this latter being brought about most commonly by swamps and stagnant waters.

Galen was the most voluminous of all the ancient writers and the greatest of the theorists and systematists. His works are a gigantic encyclopedia of the knowledge of his time, including nine books on anatomy and seventeen books on physiology (apparently, Galen was the first to dissect the muscles and describe them, probably by dissection of apes, and his writings give us the most complete picture of the anatomy and the physiology of the human body of any works handed down from antiquity); six books on pathology, sixteen essays on the pulse, the "Megatechne (Ars magna)" or therapeutics, in fourteen books; the "Microtechne (Ars parva)" or practice, and thirty books on pharmacy.

The domination which Galenic medicine held over the thoughts of men during the major part of the Christian era presents an interesting psychological problem. He constituted the Delphic oracle of medicine, and his pronouncements upon all matters relating to disease became surrounded with a false aura of infallibility. But time has dealt harshly with Galen's theories, and in the light of modern experimental medicine

his hypotheses and system of medicine have been completely overthrown. On the other hand Hippocrates, with his unfailing insistence on the value of accurate, painstaking observation and his impatience with theorizing, has grown in stature as the centuries have passed.

ANCIENT CHINESE THEORIES OF DISEASE

Medicine in China reached its highest development at about 2000 B.C. and has remained at about the same level up until very recent times. Chinese medicine is of practical interest mainly because of certain therapeutic measures which were introduced by the Chinese into Western medicine, among these being dry cupping, massage and acupuncture. The ancient Chinese are said to have practiced preventive inoculation against smallpox, and to have employed mercury for inunction in syphilis. According to Read,[31] the art of pulse feeling in China is very ancient, dating from before 500 B.C.:

> By placing three fingers side by side on the left and right wrists respectively of the patient, the Chinese physician claims to be able to obtain six indications of possible diseases in the internal organs . . . In general, the left wrist indicates diseases of the kidneys, the heart and the sexual life. The right is felt for the lungs and so forth.

Dawson's[32] article, concerned with a previously untranslated work, "Su-Wen"

or Simple Questions, by an unknown Chinese writer who probably lived prior to the end of the fourth century A.D., is of especial interest because it sums up the physiological and medical knowledge of all the preceding centuries. Curiously enough, the theories have been little, or not at all, modified and they form the foundations of present day Chinese physiology and psychology. Man is pictured as containing five viscera: (1) the heart, the seat of the vital spirit: (2) the liver, the seat of the aerial soul, which directs the internal distribution of the breath; (3) the lungs, the seat of the spermatic soul; (4) the spleen, the seat of the intelligence and of the will, and (5) the kidney, the seat of the fecundating sperm, and the procreating organ.

Disease is thought to come from a functional disorder of a viscus, and the only method for determining the sick viscus is by an examination of the pulse. Each variety of pulse (i.e. slowness, rapidity, weakness, etc.) is taught to be pathognomonic of the disfunction of a given viscus. When the sick organ has been diagnosed, dietary measures are immediately to be instituted. For example, if the heart is affected, it is because the patient has overindulged in hot and bitter foods; if the kidney is diseased, it means that cold and salty foods have been used to excess.

Dawson states:

Finally, let us speak of therapeutics. Here I call attention to an important fact. Before the Christian era the Chinese did not recognize and did not use medicaments properly speaking. So then, in ancient times, there were no medicaments properly so called, but a unique proceeding believed to heal all ills, namely the famous Chinese acupuncture. Antiquity knows only this: The invention probably dates from primitivity, for the needles for a long time were of flint. Here is the theory of acupuncture: . . . Every malady is a visceral disorder. A viscus either does or does not secrete its emanation, or does not secrete enough of it, or retains it instead of circulating it. In a word paralysis of the organ, bad work . . . Now, what does one do to the ox when he draws badly? One gives him a blow with a goad. The Chinese acupuncture is nothing else. One pricks the recalcitrant organ. The Su-Wen gives the instructions for these direct pricks, but it also indicates rather well the inconveniences and the danger of the method, if one uses the needle too violently, if one pricks ever so little to the side and so forth. The direct prick should be reserved for desperate cases, when there is nothing to lose.

In ordinary cases, indirect acupuncture should be practiced, which consists in pricking the skin area, or cutaneous district, over which a given viscus is supposed to preside:

For example, if the pulse has incriminated the heart as the offending viscus, a certain

cutaneous region of the back corresponding to the heart is pricked, whereby the heart frisks with pain and then settles down to its normal functioning.

Chapter II

ARABIC MEDICINE, THE MEDIEVAL PERIOD & THE RENAISSANCE

ANCIENT ARABIC MEDICINE

THE Islamic physicans of the eighth, ninth and tenth centuries A.D. held largely to the "humoral theory" advanced by Hippocrates and Galen to explain disease, and it is to the Arabs that Europe owes the preservation of Greek treasures and Greek science. Unfortunately, their Oriental fatalism, their contemplative brooding, their tendency to resigned submission to authority, combined with their religious belief that it is sinful to touch the human body with the hands, prevented advances in medicine that otherwise might have been made. In spite of these things, the ancient Arabs were the originators of algebra, pharmacy and geology, as well as important pioneers in certain phases of clinical medicine.

It is with somewhat of a shock of surprise that we find Mahomet almost a thousand and a half years ago saying:

> Teach science which teaches fear of God; he who desires knowledge adores God; when he spreads it, he is giving alms; he who has it becomes an object of veneration and goodwill. Science protects from error and sin; it lights the road to paradise; it guides us through the

pleasures and pains of life; it is an ornament among our friends and a shield against the enemy. The memorials of the wise alone endure because their great deeds serve as models and are repeated by the great minds who follow them. Science is the remedy for the infirmities of ignorance, a comforting beacon in the night of injustice. The study of the sciences has the value of a fast; the teaching of them has the value of prayer; in a noble heart they inspire the highest feelings and they correct and humanize the perverted.

Rhazes (860–932 A.D.) became a landmark in ancient Arabian medicine, not alone by his clinical acumen, but by his originality, as well. Not only was he the first physician accurately to describe smallpox, scarlet fever and measles, but in his famous, encyclopedic book "El Hawi" or "Continens," he advanced the remarkably modern sounding idea that fever was not a disease, but that it was an evidence that nature was at work attempting to effect a cure of the disease (23:347). In other words, he recognized fever as a symptom. Moreover, Rhazes, and after him Avicenna, introduced an entirely new conception of the etiology of the acute eruptive fevers, smallpox, measles and scarlet fever. He taught that they arose by congenital contagion, i.e. were effected by a kind of leaven, which exists in the blood of the mother and reaches the fetus through the placenta. The leaven ferments, and the blood, in its effort to purify

itself, excretes the fermenting material through the openings of the glands in the skin. Hence everyone is liable to contagion. Rhazes mentions among the diseases "which are transmitted from one person to another lepra [elephantiasis?] itch, consumption, and pestilential fever." These, he says are infectious "when one is shut up in a narrow house with those afflicted thereby or when one sits upon their windward side."

That Rhazes was not alone a clinician and a theorizer, but an observing experimentalist, is testified to by the fact that when he wished to study the effects of mercury he fed some to a monkey, and he gives the results of his experiment as follows:

> As to pure mercury, I believe it not to be very pernicious; it gives rise to intense abdominal and intestinal pain, but afterwards leaves the body as it entered it, especially if the subject takes exercise. I gave it to a monkey that I had at my house and things passed as I have said. I noted that he twisted himself about, clenched his teeth, and pressed upon his belly with his hands. Calomel, and especially sublimate, are very dangerous and very active poisons. They cause very sharp abdominal pains, colic and bloody stools. The emanations of mercury give rise to paralysis.[33]

The "Almaleki" or "Maliki" (Royal Book) of Ali Abbas (who died in 994 A.D.) and the "Canon" of Avicenna (980–1036

A.D.) were encyclopedic volumes on medicine which were widely used in the schools of Europe down to the beginning of the eighteenth century. Ali Abbas marked somewhat of an advance on Rhazes by effecting a rather clean-cut distinction between wind-borne diseases and those which are simply infectious. Avicenna, known as the "Prince of Physicians," is reputed to have died at the age of fifty-six years as a result of over-dalliance along the primrose path of pleasure. Yet Avicenna is said to have written over one hundred books on various subjects; his wonderful description of the origin of mountains entitles him to being called the "Father of Geology"; he was the first to describe the guinea-worm; and his "Canon," in which he attempted to reconcile the medical knowledge of his time with the teachings of Galen and Aristotle, became the great fountain head of scientific authority during the Middle Ages, not alone in the Orient, but in Europe as well. Avicenna recognized the contagiousness of leprosy and variola, but he followed the Hippocratic school in laying especial emphasis upon fermentations of body humors and on the corruption of the air as the etiologic agents of disease.

Geber (702–765 A.D.) was a famous early Arabian alchemist. Alchemy, often referred to as the forerunner of chemistry, was really the chemistry of ancient and

medieval times. To Geber, during the course of his search for potable gold, is attributed the discovery of nitric acid, sulphuric acid and aqua regia. He held the opinion that everything is made of mercury, sulphur and salt. Moreover, accepting the current theory of planetary control over the various organs of the body (the heart was said to be ruled by the Sun, the brain by the Moon, the liver by Jupiter, the spleen by Saturn, the lungs by Mercury, the bile by Mars, and the kidneys by Venus), he taught that the seven planetary metals: gold, silver, tin, copper, quicksilver, iron and lead had a specific curative action upon these respective organs, subject to the will of the stars. It is interesting to observe that Paracelsus, as late as the sixteenth century, not alone gave a new direction to alchemy by his insistence that its proper function was the finding of new medicines rather than the making of gold, but was a staunch adherent of Geber's ideas.

Affording an interesting sidelight upon the behavior of Arabian physicians of his day, is the following quotation[34] from Prascianus, who lived during the latter half of the fourth century and the first half of the fifth century A.D.

As the patient lies on his bed prostrated by the severity of the disease, there quickly comes into the room a crowd of us physicians. No feeling of sympathy for the sick man have we,

nor do we realize how important we all are in the presence of these forces of nature. Instead we struggle to the utmost of our ability to obtain charge of the case; one depending for success on his powers of persuasion, a second on the strength of the arguments which he is able to bring forward, a third on his readiness to agree with everything that has been said, and the fourth on his skill in contradicting the opinion of everybody else. And, as this quarrel goes on, the patient continues to lie there in a state of exhaustion. "For shame!" Nature seems to say, "you men are an ungrateful lot! You do not even permit the patient to die quietly; you simply kill him. And then, moreover, you accuse me of not furnishing sufficient means of effecting a cure. Illness is certainly a painful affair, but I have provided plenty of remedies. Poisons, I admit, are hidden in some of the plants, but the healing agents which may be extracted from them are much more numerous. Away then, with your angry disputes and your self-glorifying chatter; for in these are not to be found the remedial agents which I have bestowed upon man, but rather in the powerful forces which reside in the seeds, fruits, plants and other objects which I have created in his interests."

And indicative of Mohammedan practice at a considerably later date, toward the end of the fourteenth century, the period usually assigned for the composition of the "Arabian Nights," we take the following description from Garrison:[35]

The Arabian physician, whose professional importance was gauged by the height of his

turban and the richness and length of his sleeves, was usually an astrologer and a magician, who regarded the heart as "the prince of the body," the lungs as the fan of the heart, the liver as the guard of the heart and the seat of the soul, the pit of the stomach as the seat of pleasure and the gall-bladder as the seat of courage.

Ibu al Khatib (1313–1374 A.D.), writing of the plague and its prophylaxis, advised "a disinfection of the circumambient air by good, clean smells, by flowery perfumes, etc." and "the avoidance of the places where one may expect corruption from those sick and dead of the disease, *their clothes, vessels and utensils*, avoidance of entry into an infected house or of approach to the neighborhood of the sick, or, if this be impossible, the visit must be rapid and accompanied by every precaution."

THE MEDIEVAL PERIOD (1096–1438)

During the Medieval Period, reasoning in medicine was largely formal and deductive; instead of questioning nature, argument and dialectic subtleties were the order of the day. "Logic, which for us is but a drill, and, like all drills, a little cut of fashion, was for the Middle Ages a means of discovery, nay, the very source of truth . . . The dialectically irresistible was the true." (Allbutt.[36])

Galen's teachings held almost absolute and sacred sway, whereas there was an almost complete neglect and ignorance

of the teachings of Hippocrates. From the time of Galen up to about the eleventh century, when the medieval schools of medicine began to arise, progress in scientific thought had been almost nil. The effect of Christianity becoming the State religion had been to stifle science; for pagan magic had been substituted priestly laying-on of hands and exorcism, and for pagan superstition had been substituted Christian prayer. The Middle Ages afflicted medicine with theological chemistry, and belief in sorcery, demoniacal influences and the stars was general. Probably as a result of the fact that most of the Fathers of the Christian Church rejected earthly means of healing, faith in the power of saintly relics to heal disease grew to such an extent that, during the sixth century A.D. such faith had become almost universal. So great was the effect produced upon the minds of the people by the public display of such objects as bones of saints, portions of their gravestones, etc., that many marvelous cures were reported as the result of such displays, even as recently has happened in Massachusetts. With the rise of the School of Salerno, around the year 1000 A.D., and the School of Montpellier (1220 A.D.) a little light was brought into European medicine, but only enough to accentuate the prevailing darkness.

The thirteenth century witnessed the

emergence of three great scientific figures, Theodoric, Mondeville and Roger Bacon, intellectual pioneers who, although they did not greatly influence contemporary thought, became living beacons who pointed the road along which modern medical science has gone.

Theodoric and Mondeville. Teodorico Borgognoni, 1205–1296 A.D., Bishop of Cervia, and Mondeville (1260–1320 A.D.) were surgeons who strongly contradicted the Galenic dogma of "laudable pus." How advanced they were is indicated by the fact that they, with the exception of Paracelsus, were the only opponents of this pernicious dogma until Lister (1865). Theodoric said:

> For it is not necessary, as Roger and Roland have written, as many of their disciples teach, and as all modern surgeons profess, that pus should be generated in wounds. No error can be greater than this. Such a practice is indeed to hinder nature, to prolong the disease, and to prevent the conglutination and consolidation of the wound.

And Henri de Mondeville staunchly advocated the prevention of suppuration by simple cleanliness. Some of his utterances are well worth remembering, not alone for their common sense, but as well for their caustic wit:

> God did not exhaust all of his creative power in making Galen . . . Many more surgeons

know how to cause suppuration than to heal a wound . . . Keep up your patient's spirits by music of viols and ten-stringed psaltery, or by forged letters describing the death of his enemies, or by telling him that he has been elected to a bishopric, if a churchman . . . Never dine with a patient who is in your debt, but get your dinner at an inn, otherwise he will deduct his hospitality from your fee.[37]

Roger Bacon was born about 1210 A.D. in England, in the hamlet of Ilchester, Somersetshire, and received his early training at Oxford. At the age of thirty he went to Paris to study, and after seven years of most painstaking study of the various branches of learning he received the doctor's degree. His fondness was particularly for mathematics and chemistry and physics. His discoveries in optics, particularly, (he is credited by many as being the discoverer of spectacles) were pronounced by his contemporaries works of the Devil and he was subjected to persecution, punishment and deprivation. Finally, in 1266, Pope Clement IV granted him a dispensation, under a vow of absolute secrecy, to continue his researches unhindered. He died in 1294.

Bacon wrote very little on medicine and he attributed a false importance to astrology, going so far as to say that astrology is the best part of medicine. His numerous and varied writings proclaim him, however, a most advanced

scientific thinker. Living in an age when so much of the current "knowledge" was merely a specious cloak that hid fundamental ignorance, he wrote: "The four obstacles to knowledge are authority, prejudice, habit, and a false conceit of knowledge." Worthy of being inscribed on the facade of every modern scientific laboratory are his words: "Experiment is a firmer and more trustworthy basis of knowledge than argument." And where in all literature, will one find a finer description of the true man of research, than is to be found in the words written by Roger Bacon concerning his friend Peter of Maricourt?

One man I know, and one man only, who can be praised for his achievements in this science. Of discourses and battles of words he takes no heed . . . What others strive to see dimly and blindly, like bats in twilight, he gazes at in the full light of day, because he is a master of experiment. Through experiment he gains knowledge of natural things, medical, chemical, indeed of everything in the heavens and earth . . . As for reward, he neither receives nor seeks it. If he frequented kings and princes he could easily find those who would bestow on him honors and wealth. Or, if in Paris, he would display the results of his researches, the whole world would follow him. But since either of these courses would hinder him from pursuing the great experiments, in which he delights, he puts honour and wealth

aside, knowing well that his wisdom would secure him wealth whenever he chose.

Bacon then goes on to say:

> The wiser men are, the more humbly will they submit to learn from others; they do not disdain the simplicity of those who teach them; they are willing to lower themselves to the level of the husbandman, of poor women, of children. Many things are known to the simple and unlearned which escape the notice of the wise. I have learned more important truths beyond comparison from men of humble station, who are not named in the schools, than from all the famous doctors.

During the Medieval Period, Europe was swept with plagues and epidemics of wider variety and greater severity than it knew before or has known since. The earliest of the great medieval pandemics were leprosy, ergotism (857 A.D.), scurvy (1250), influenza and "dancing mania" (epidemic chorea); the most terrible were the Black Death (bubonic plague) and syphilis. These diseases were variously attributed to comets, astral influences, to storms, the failure of crops, the sinking of mountains, the effects of drought or inundation, swarms of insects, poisoning of wells by the Jews and other absurd causes. Syphilis, in addition to these causes, was attributed to intercourse of a leper with a prostitute (Monardi and Paracelsus), poisoning of the wells by the Spanish viceroys of Naples

(Fallopius) or to human flesh eaten by the French for ordinary meat (Fioravanti).

Of leprosy, the following passage occurs in the Luneburger Chronik, as paraphrased by Heinrich Heine:[38]

> Living corpses, they wandered to and fro, muffled from head to foot; a hood drawn over the face, and carrying in the hand a bell, the Lazarus-bell, as it was called, through which they were to give timely warning of their approach, so that everyone could get out of the way in time.

Of the Black Death, the great pandemic of bubonic plague which devastated Europe in 1348, the following account is given by a contemporary writer:[39]

> Shrift there was none; churches and chapels were open, but neither priests nor penitents entered—all went to the charnel-house. The sexton and the physician were cast into the same deep and wide grave; the testator, and his heirs and executors were hurled from the same cart into the same hole together.

And during the epidemic of St. Vitus' dance, which appeared in Europe in 1374, throngs of from 200 to thousands of convulsionaries went from town to town, contaminating others with the chorea from which they were suffering. And after the Black Plague of the Middle Ages, bands of flagellants went about Europe, singing hymns of penitence and imposing mortification upon themselves to appease the wrath of heaven.

During the twelfth and thirteenth centuries the study of the pulse and examination of the urine formed the basis of the practical teaching in such medical centers as Salerno. The urine was examined in the morning; if it was of a lemon yellow color, bile predominated; if it was thick and red, blood predominated; phlegm predominated if it was thick and white; and atrabile if it was simply white. A urine which was in a medium condition between these four indicated a perfect state of health.

It should be noted that in the beginning of the fourteenth century human dissections were made at the Universities of Padua and Bologna, and thereby gradual knowledge of anatomy was gained, which culminated in the monumental researches of Vesalius.

THE PERIOD OF THE RENAISSANCE. THE REJUVENATION OF SCIENCE (1438–1600)

During the Renaissance certain scientific figures arose as though in affirmative answer to the utterances of Roger Bacon. Of the scientific path-breakers of this period, peculiar eminence rightfully belongs to four men: Paracelsus, Fracastorius, Vesalius and Paré, each of whom, by his scientific contributions, helped to prepare the soil out of which a more rational and accurate concept of the nature of disease processes was slowly to germinate.

Paracelsus (1493–1541). There are few more intriguing figures in the whole history of science than Paracelsus, or Aureolus Theophrastus Bombastus von Hohenheim, as his full name reads. A Swiss mountaineer, son of a physician, friend of barbers, executioners, gypsies, midwives and fortune tellers, he had an intractable liking for low company. As he says in one of the many treatises which he wrote. [Paragranum—Grain of Superior Quality][40].

> By nature, and also owing to the kind of people with whom I associated in my youth, I am not of a finely-spun texture . . . We were not nourished with figs and white bread, but with cheese, milk, and black bread, food that does not make delicate lads . . . They say of me that I lead people astray, that I am possessed of a devil, that I am a sorcerer, and that I am a magician. Whatever truth there may be in these charges, one thing is certain: You are all of you unworthy to unloose the latchets of my shoes.

In another connection, he once wrote: "My poverty was thrown in my face by a Burgomaster who had perhaps only seen doctors attired in silken robes, never basking in tattered rags in the sunshine. So it was decreed I was not a physician."

In Paracelsus the teaching of Galen met its first great enemy. In fact, the consuming ambition of Paracelsus' life was to overthrow the Galenic idol and

Paracelsus.
(1493–1541)

it is not at all surprising to find him in 1527 signalizing his appointment as city physician of Basel by publicly burning the works of Galen and Avicenna, and protesting that his shoebuckles were more learned than these famous authors of antiquity. A year later, a quarrel over fees forced him to flee the city; he then wandered and practiced medicine all over Germany and died, in 1541, at the age of forty-eight. According to his enemies, his death resulted from the effects of injuries received in a tavern brawl in Salzburg.

Before entering upon a description of his ideas concerning the nature of disease, and before attempting an analysis of his actual accomplishments, it will be illuminating to consider the peculiar method of acquiring knowledge which Paracelsus advocated and practiced. In the first place he attached no value to mere scholarship; scholastic disputations he utterly despised with the wholehearted ardor of his intolerant nature. All medical traditions and all medical "authorities" except Hippocrates, of whom he spoke with respect, he ground under the heavy heel of his scorn. He said that most medical discussions turned upon definitions and theories rather than upon actual practice. To learn medicine properly one must wander, studying the humors and passions and diseases of various nations, as he did. "Whence have I all my secrets,"

he asked, "out of what writers and authors? Ask rather how the beasts have learned their arts. If nature can instruct irrational animals, can it not much more man?" Paracelsus believed that by intuition man could come to intimate knowledge of God and all living things, because from God all things are received; man creates nothing. Hence the contempt held by Paracelsus, and the theosophists who followed him, for all knowledge obtained by work and application, and his pride in wisdom obtained directly from God.

But having been the first to make a clean sweep of dogmatic medicine, having discarded Galenism and witchcraft and uromancy and uroscopy, and having insisted that clinical therapeutics be substituted for theory and dogma and scholastic discussion, Paracelsus proceeds to expound a dogma of his own. To know the nature of man and how to treat it, men should study not anatomy, which Paracelsus scorned, but all parts of external nature. Life, he taught, was controlled by the Archaeus, a universally germinative force, which was principally seated in the belly, but was also distributed throughout the body. Diseases, according to Paracelsus' mystical concepts, were not natural, but were spirits, essences of real entities which enter the body. By what intellectual legerdemain did Paracelsus, who tilted such valiant lances against witchcraft

and superstition and "theorizers," reconcile the strange compost of mystical theorizing which he advanced? Diseases, he taught, arise from five main causes: (1) from astral entities, which leave within the body imprints of changes produced by the stars; (2) from entities or poisons contained in foods; (3) from natural entities controlled by astral entities; (4) from entities that are the spirits and the demons and (5) from entities that represent the immediate effects of the acts of God upon us.[41] Because disease is not natural but spiritual, Paracelsus held that nature sufficed for the cure of most diseases, but that when it became necessary for the physician to interfere, a drug or remedy should be employed, whose action was not directed against the disease itself, but against the spiritual seed of the disease. These remedies he called "arcana," which implied not alone a specific action, but suggested a mystical connection between the remedy and the essence of the disease as well; from this, through phases of increasing complexity, arose his doctrine of "signatures," which presupposed a connection between every part of the world of man and the world of nature. Paracelsus was the first publicly to teach that each drug contains a specifically active elementary body or "quintessence" which could be

extracted, and for this reason he preferred tinctures (alcoholic extracts).

Paracelsus also maintained that the human body is composed of sulphur, mercury and salt; he held that disease results when the mercury becomes precipitated, distilled, or sublimated in the body, or when the sulphur becomes coagulated or dissolved, or when the salt becomes calcinated or alkalified.

Although technically not a chemist, and although he made no outstanding chemical discoveries, yet he made opium, still known by the name laudanum, which he gave it, mercury, lead, sulphur, iron, arsenic, and potassium sulphate (called the "specificum purgans Paracelsi") a part of the pharmacopeia. From the clinical standpoint, Paracelsus was the first to write on miner's (occupation) diseases and apparently he was the first to establish a correlation between cretinism and endemic goiter. In regard to syphilis, he taught that the disease was divided into stages and he observed its heredity. But he falsely believed gonorrhea to be an initial stage of syphilis, and therefore called it French Disease.

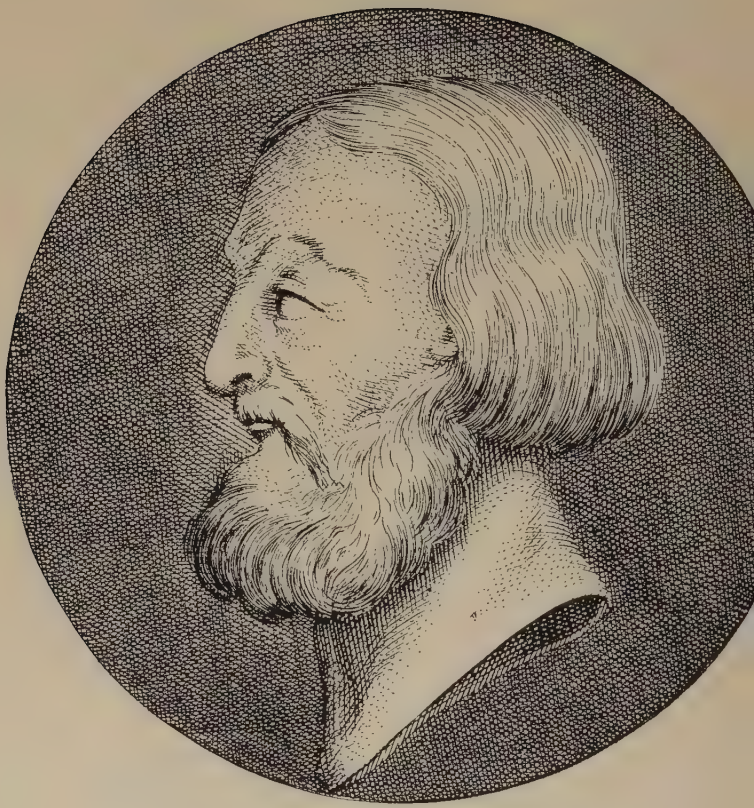
A vivid, baffling personality, this man Paracelsus. One can almost see him with his tongue in his cheek as he writes the following passage in his "De Pestilitate":

> But if a witch desires to poison a man with her eyes, she will go to a place where she

expects to meet him. When he approaches, she will look into the poisoned mirror, and then, after hiding the mirror, look into his eyes, and the influence of the poison passes from the mirror into her eyes, and from her eyes into the eyes of that person; but a witch may cure her own eyes by making a fire and staring into it, and then taking the menstrual cloth, and after tying it around a stone, throwing it into the fire. After the cloth is burned, she extinguishes the fire with her urine, and her eyes will be cured; but her enemy may become blind.

Fracastor (1483(1478?)–1553). Fracastor, also known as Fracastorius and Fracastoro, is distinguished by two striking contributions which he made to the elucidation of the nature of infectious disease. He was the first clearly to distinguish the three categories of infection: by contact, by fomites, and at a distance; and he enunciated a curiously advanced doctrine of infection from hidden *seminaria* or seeds which, in many respects, constituted a rather remarkable prophecy of the modern germ theory of disease.

Fracastorius was born at Verona and died near there. He was the first scientist to refer to the magnetic poles of the earth; he gave the first good scientific description of typhus fever, and was the author of the most celebrated medical poem that has ever been written, "Syphilis sive de morbo gallico" (Venice 1530), in which,



Girolamo Fracastoro.
(1483?–1553)

for the first time, the venereal nature of the disease was taught, and in which, also, the name syphilis was first given to the disease. In 1546, in his treatise "De Contagionibus," Fracastor considered the clinical nature of syphilis, describing it as a contagious affection acquired during coitus, and stating that it begins with small ulcers on the genital organs, soon followed by a generalized eruption. He also refers to gummata, exostoses, loss of hair, etc.

In this same treatise ("De Contagionibus"), Fracastor states his belief that the cause of contagious maladies is to be found in *seminaria contagionum*, seeds of contagion which he believes to be capable of reproduction in suitable media. He does not directly refer to them as *contagia animata* (living organisms), but the fact that he considered them to be capable of multiplication has led many historians to the belief that Fracastor, by a kind of unexplained clairvoyance, visioned the modern germ theory of disease, in spite of the fact that he assumed the spontaneous generation of the seminaria. A young contemporary, Hieronymo Mercuriali, wrote of him in 1577: "It was he who first opened man's eyes to the nature of contagion."[28] In Book 1, Chapter 12 of his "De Contagionibus," Fracastor writes:

As has been said there is a power in these seeds that they may multiply and propagate their like. Those causes which produce obstructions,

plethoras and corruptions of the humors by which they become fouled, putrified and occluded give rise to seeds that can convey the infection to others, whether the same causes and dispositions be acting in those others or not, whence they may carry the same contagion to a second and third. But the essence and seminaria of contagion may also come to us from an extrinsic source. Thus we see diseases spreading in the population as a whole. Epidemics, as they are called, of which some, though not contagious, may affect many cities or regions and are then called communes; others again of these are contagious and pass from one to another without atmospheric disposition, these are called non communes.

Fracastoro divides contagious diseases as follows: (Viktor Fossel's version, Leipzig, 1910).

(1) Those which infect only by contact; (2) those which infect by contact and by fomites as scabies, phthisis, areae, leprosy (elephantiasis) and their kind. I call fomites such things as clothes, linen etc. which although not themselves corrupted, can nevertheless foster the essential seeds (seminaria prima) of the contagion and thus cause infection; and (3) those which infect not only by direct contact, or through the agency of a residuary centre or focus of infection, but also those which are capable of spreading their infective elements over wide areas, for instance, the pestilential fevers, certain ophthalmias, variolas, etc.

In speaking of infection by means of fomites, Fracastor writes (Book 1, Chap. 4):

It may be questioned whether the infection of a fomes is of the same nature (as infection that acts only by actual contact). The nature of infection by a fomes appears, indeed, to be different since having left its original focus and passed into a fomes it may there last for long unchanged. It is, indeed, wonderful how the infection of phthisis or pestilential fevers may cling to bedding, clothes, wooden articles, and objects of that kind for two or even three years, as we have ourselves observed.

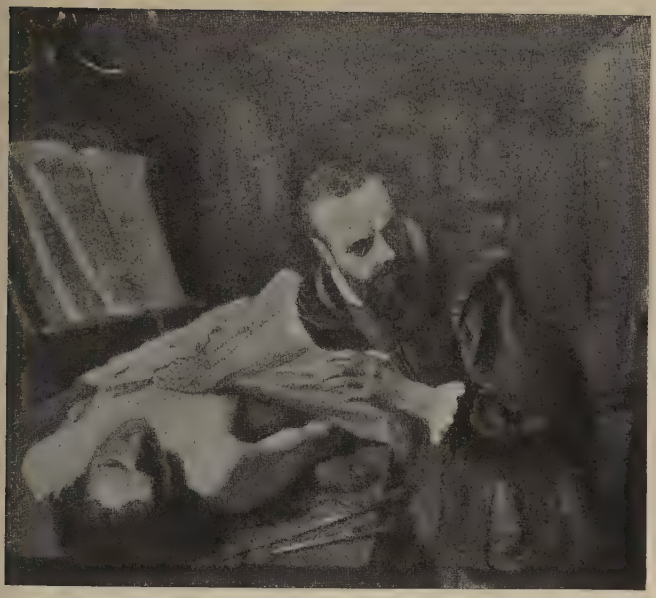
Concerning the affinities of infections (Book 1, Chap. 8) he says:

The affinities (analogiae) of infections are numerous and interesting. Thus there are plagues of trees which do not affect beasts and others of beasts which leave trees exempt. Again among animals there are diseases peculiar to men, oxen, horses and so forth. Or, if separate kinds of living creatures are considered, there are diseases affecting children and young people from which the aged are exempt and vice versa. Some again only attack men, others women, and others again both sexes, There are some men who walk unharmed amid the pestilence while others fall. Again there are infections which have affinities for special organs. Thus ophthalmia affects only the eye. Phthisis has no effect upon that most delicate organ, but acts especially upon the lungs . . . Alopeciae and Areae confine themselves to the head.

Vesalius (1514–1564). Until the middle of the sixteenth century, anatomy and physiology had remained much the same as taught by Galen. As a natural consequence, man's ideas of the nature of disease awaited acquisition of real knowledge concerning the structure and functions of the human body.

Among the important fore-runners of Vesalius should be mentioned Mondino de Suzzi, whose Anathomia was first published in Padua in 1487, but which was completed in 1316; Leonardo da Vinci (1452–1519), the greatest artist of the Italian Renaissance and characterized by William Hunter as "the greatest anatomist of his epoch"; and Berengarius de Carpi (1470–1550), who was the first to substitute anatomical drawing from nature for schematic representations of organs and structures.

Andreas Vesalius, the father of modern anatomy and the man who made dissecting respectable, was the most commanding figure in European medicine between Galen and Harvey. He was a Belgian, born in the little town of Wesele, from which his name is derived. His epoch-making work, "De Fabrica Humani Corporis," published in 1543 in Basel, before its author was twenty-nine years of age, marked the definite beginning of the overthrow of Galen's doctrines, and was actually a re-creation of the whole gross anatomy of the human body. The effect



Andreas Vesalius (1514–1564) dissecting a body in secret.

of Vesalius' exposure, by means of actual dissection of the human body, of the numerous errors in Galen's scheme of anatomy, was positively revolutionary, because Galen had held almost despotic sway over physicians for more than one thousand years. Not alone did Vesalius' volume deal with the anatomy of the human body, but it contained information on physiology, pathological anatomy and comparative anatomy.

In exposing Galen's erroneous teaching that the blood passes through certain hypothetic pores in the ventricular septum of the heart, through which food and air were supposed to be mixed, Vesalius cynically writes: "We are driven to wonder at the handiwork of the Almighty, by means of which the blood sweats from the right into the left ventricle through passages which escape the human vision." Galen, moreover, had described, in the intraventricular septum of an elephant, a small, lyre-shaped bone, which he named the "incorruptible bone"; he affirmed that this bone was present in the hearts of animals and of man, although he had never dissected the human body. Vesalius was the first to demonstrate the non-existence of this bone in the heart of man.

Opposition to Vesalius was extreme; when Vesalius showed that the human thigh bones are straight, and not curved

as taught by Galen, Sylvius, his old teacher, bitterly opposed him, and asserted "that the straight thigh bones which, as every one saw, were not curved in accordance with the teaching of Galen, were the result of the narrow trousers of his contemporaries, and that they must have been curved in their natural condition, when uninterfered with by art."[42]

Servetus (1509–1553), a contemporary of Vesalius, and the discoverer of the pulmonary circulation (1553), was a living fagot thrown on the pyre of Calvin's intolerance.

After Vesalius came his disciples Eustachius and Fallopius, who made most important contributions to the knowledge of anatomy. Eustachius was the first to discover the Eustachian tube, the thoracic duct and the suprarenal bodies (1563), he was also the first accurately to describe the uterus. To Fallopius belongs credit for the discovery of the semicircular canals, the ovaries, and round ligaments, and the trigeminal, auditory and glossopharyngeal nerves.

The circumstances surrounding the last years of Vesalius were in pathetic contrast to the scientific contributions that he made. Oppressed with a sense of failure but still dreaming that he might "once more be able to study that true Bible, as we count it, of the human body, and of the nature

Michael Servetus.
(1509–1553)

of man" he died alone, and almost unknown, on the friendless island of Zante.

Paré (1510–1590). The direct influence of Vesalius on Renaissance surgery is well illustrated in Ambroise Paré, that fascinating barber's apprentice who came up from the provinces to Paris at the age of nineteen and lived to become the greatest army surgeon, and chief surgeon to four successive kings of France; Henry II, Francis II, Charles IX and Henry III. In the three large volumes of Paré's writings (Malgaigne's Edition) occurs frequently his famous saying, which is carved on his tomb; "Je le pansay, et Dieu le guarist" (I dressed him, and God healed him). In speaking of his treatise on Surgery, Paré wrote:

> My professional brethren must not expect to find any new and startling facts, but simply here and there some little addition to our previous stock of knowledge; for the good Guy de Chauliac has taught us that we are like the child who sits astride the giant's neck; that is, we can see all that he sees and just a little more, or, in other words, we are able, through the aid afforded by the writings of our predecessors, to learn all that they have learned, and may at the same time acquire a little further knowledge through our own observations.

And in his "Apology,"[43] in defending himself against a critic who condemned his use of the ligation of vessels in surgical operations, Paré wrote:

Ambroise Paré.
(1510–1590)

I will say you are like the young lad of Low Brittany, plump-buttocked and thickset, who demanded leave of his father to come to Paris to learn French. When he arrived, the organist of Notre Dame found him at the gate of the Palace, and took him in to blow the organ, where he was three years. Finding he could speak French somewhat, he returned to his father telling him that he could speak good French, and, moreover that he knew how to play on the organ. His father received him very joyfully, because he was so wise in so short a time. He went to the organist of their great church, and prayed him to permit his son to play on the organ, to the end that he might know if his son was as good a master as he said he was, which the master organist accorded willingly. Coming to the organ he threw himself with a great leap to the bellows. The master organist bade him play and that he would blow for him. Then this good organist said to him that he knew nothing else than how to blow. I believe likewise, mon petit maistre, that you know nothing else but to cackle in a chair, but I will play on the keys and make the organ resound, that is to say that I will perform the operations of surgery, that which you know not at all how to do, because you have not budged from your study and the schools, as I have said!

We cannot pause to dilate on Paré's numerous original contributions to surgery and obstetrics (he was the inventor of many surgical instruments, was the first to perform exarticulation of the elbow joint, and was the first to popularize the

truss in hernia). But something more directly applicable to our subject is found in the fact that Paré, by his example in giving up the use of boiling oil in the treatment of gunshot wounds, and substituting the ligature, became the pioneer asepsist, although it has been said that he persisted in the use of a salve made of "fat of puppy dogs." Moreover, Paré was superstitious, and he believed in astrology, magic and witchcraft. In referring to the plague, he wrote:

> The plague is a disease coming of the wrath of God, furious, sudden, swift, monstrous, dreadful, contagious, terrible, called by Galen a wild beast, savage and most cruel; the mortal enemy of the life of men and of diverse sorts of beasts, plants and trees . . . So let it be agreed that the plague, and other dangerous maladies, are evidence of the wrath of God against the sins, idolatries and superstitions which reign over the earth; as even a profane author (Hippocrates) is compelled to confess that there is something divine in diseases.

Dr. Howard Kelly[44] suggests that Paré may have been the first to consider flies as possible transmitters of infectious diseases.

It is of decided interest, in closing this brief consideration of the Renaissance Period, to attempt to classify the four outstanding scientific figures of the period. Paracelsus, great though his personal influence was, was not a scientist in the

modern meaning of the term; he was, rather, a militant enemy of all authority and all dogma, who reserved to himself the right of being a dogmatist. As proponent of a mystical theory of disease, which lacked the solid foundation of either experiment or accurate observation, he retarded, rather than advanced, the struggle which man has waged since pre-history to obtain a true conception of the nature of the diseases that afflict him. On the other hand, by his insistence that the body tends to "cure" many diseases in spite of, rather than because of, officious medical meddling, by his vigorous opposition to magic and superstition and sacred "authority" in medicine, as well as by his other contributions in the field of practical therapeutics, Paracelsus made definite contributions to the progress of medical thought. Fracastorius, in addition to venturing a curiously prophetic guess as to the cause of infectious diseases, distinctly advanced medical knowledge of a specific disease, syphilis, and widened the range of man's conceptions of disease in general by his pioneer classification of contagion. Paré's main contributions were in the field of surgery, and his major influence lies in the fact that his innovations in the treatment of wounds entitle him to consideration as the pioneer asepsist. In contradistinction to these three, Vesalius was a genuine scientist. By his accurate

anatomical researches he laid the solid foundation of a knowledge of the structures and functions of the human body upon which alone a knowledge of the nature of disease processes can be based. It should also be noted that Guillaume de Baillou (1538–1616), the French physician, was the first to describe whooping cough, and was also the first to use the word rheumatism in its modern sense, and to differentiate this latter disease from gout.

It must, however, be emphasized that Paracelsus, Fracastorius, Vesalius and Paré were rather extraordinary luminaries in the still widespread darkness of medicine and surgery. During the Renaissance, and even during the seventeenth century, the practice and theory of medicine in Europe remained largely enslaved by Galen. Blind adherence to Galenic teachings, even when such teachings were proved erroneous, remained the order of the day, and, to a great extent, Paracelsus and Vesalius were unheeded voices crying in the scientific wilderness. The ordinary run of physicians, who were almost invariably pictured by contemporary painters as gravely inspecting a urinal, remained rooted in their belief in astrology and amulets, and most of the surgeons, in the words of William Clowes (1540–1604), who was probably the greatest surgeon during the reign of Queen Elizabeth, "were no better than runagates

or vagabonds . . . shameless in countenance, lewd in disposition, brutish in judgment and understanding."

Illustrative of the state of medical knowledge regarding bubonic plague during the latter part of the fifteenth century, the tract of Bengt Knutsson, Bishop of Arusiens, published probably in 1485, is most illuminating.[45] According to Vine, this work on the plague was the source of all the treatises on the subject for 150 years. Its author, Bengt Knutsson (Benedict Kanuti) had practiced medicine at Montpellier prior to his election as a bishop of Västerås in 1461. Under the heading of "The tokenes of this Infirmite" the author says:

The first is whan in a sommers daye the Wedyr often times chaungeth, as in the morning the Wedyr appereth to rayne; afterward it apperith cloudy and at last wyndy in the south.

The second tokyn is whan in sommer the dayes apperith al derke and like to rayne and yet hit rayneth not; and if many dayes so continue it is to drede of grete Pestilence.

The thirde tokyn is whan grete multitude of flyes ben upon the erthe thenne it is signe the ayer is venemous and enfect.

The fourth token is whan the sterres (stars) semen ofte times to falle; then hit is token that the ayer is enfecte with moche venemous vapours.

The v token is whan a blasyng sterne is see in the element; thenne it sholde fortune sone after to be grete manslaghter in bataylle.

The vi token is whanne there is grete lyghtnynge and thundre namely oute the southe.

The vii token is whan grete wyndes passen out of the south they be foule and unclene, therefore whan these tokens appere it is to drede grete pestilence but god of his m'cy (mercy) will remeve it.

The author next proceeds to a consideration of the causes of pestilence, and says:

These thinges folowyng be the causes of pestilence:

The Pestilence cometh of thre thinges, so time it cometh fro the rote bynethe, other while fro the rote above, so that we may fele sensibly hone the chaunge of the ayer appereth unto us, and somtyme it cometh of both togidr, as wele fro the rote above as fro the rote bynethe. As we see a sege or privy next to a chambre or of any other particular thyng whiche corrupteth the ayer in his substance and qualite, whiche is a thinge may happe every daye and ther of cometh the ague of Pestylence. And aboute the same many phisicions be deceyved, not supposying this axes (accident) to be a Pestilence; so time it cometh of dede careyn (carrion) or corrupcion of standing waters in diches (ditches) or slouhes and other corrupt places, and these thinges somtyme be universall and somtime particular. From the rote above it fortuneth the causes of the bodyes above in the ayer by whome the spyryte (spirit) of lyfe ys corrupte in a man or in a beste. In like wyse as Auycenne

(Avicenna) sayth in his fourthe boke: By the forme of the ayer above the bodyes benethe lightly be infecte. For the impressyons above corrupteth the ayer and soo the spirytes of a man ben corrupte. This infirmite cometh also from the rote above and bynethe. Whanne of the impressions above the ayer is corrupt, and of the putrefaccion or rotyn careyn of the vyle places bynethe, an infirmite is caused in a man, and suche an infirmite sometime is an axes, sometime a postume or a swellyng, and that is in many thinges. Also the ayer inspired somtime is venemous and corrupt, hurtyng the herte that nature many wayes is greved, so that he perceyveth not hys harme. For the uryne appereth fayer and she beth [of] gode dygestion, yet neverthelesse the pacyent is lyke to dye. Wherfore many phisycions seying (seeing) the uryn of their pacyents, they speke supficially [superficially] and be deceyved. Therfore it is nede, that every pacient provyde to himselfe a gode and expert phisycion. These thynges wryton before are the causes of Pestilence. But aboute these thynges two questions be meoved. The first is wherfore one dyeth and another dyeth not in a towne where men be dede in one hous and in another hous ther dyeth none. The second questyon is: whether pestilence sores be contagious. To the firste questyon I say it may happe to be of two causes, that is to saye of that thyng that doth and of that thyng that suffreth. An ensample of that thyng that doth: the influence of the bodyes above beholdeth that place or that place more than this place or this place, and the pacient is more disposed to dye than another. Therfore it is to be noted

that bodyes be more hote [hot] disposed of oopyn poorys [open pores] than bodyes in fect havyng the poores stopped with many humours. Where bodyes be of resolucion, or opening, as men whiche abusen themselfe with wymmen, or usen oftentimes bathis, or men that be hote with labour or grete angre, they have their bodyes more disposed to this grete sekenes. To the second question I saye that pestilence sores be contagious by cause of enfecte humours bodyes, and the reek or smoke of suche sores is venemous and corrupteth the ayer. And therefore it is to flee fro suche persons as be infect. In Pestilence time no body sholde stande in grete prece (press) of people, be cause some man of them may be infect. Therefore wyse phisicyens in visityng seke folke stande ferre fro the pacient, holdyng their face toward the doore or wyndowe. And so sholde the servauntes of seke folke stande. Also it is gode to a pacient every daye to chaunge his chambre and often times to have the wyndowes opene agenst the north and eest and to spere the wyndowes agenst the south, for the south wynde hath two causes of putrifaction. The firste is it maketh a man, beyng hole or seke, feble in their bodyes. The seconde cause is, as it is writon in the second (book) of Aphorismus, the southe wynde grevyth the heering and hurteth the herte by cause it openeth the poores of man and entreth into the herte. Wherfore it is gode to an hole man in tyme of Pestilence when the wynde is in the south to be within the hous al daye and if it schal be nede a man to goo oute, yet lete hym abide in hys hous untyl the sonne be up in the eest passyng southward.

Chapter III

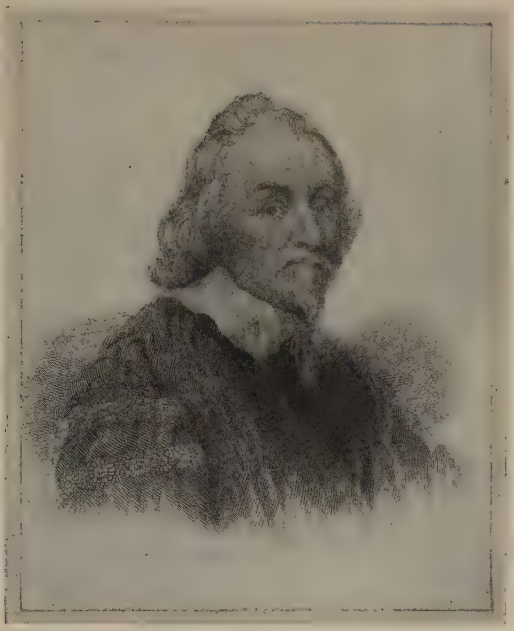
THE SEVENTEENTH AND EIGHTEENTH CENTURIES

THE SEVENTEENTH CENTURY

HARVEY (1578–1657). *The Pioneer Physiologist.* Just as Vesalius, in the sixteenth century, marked an epoch by his anatomical researches on the organization of the human body which were to undermine the Galenic teachings and establish modern anatomy, so in the seventeenth century Harvey's demonstration of the circulation of the blood signalized the epoch of the beginnings of modern physiology. Between the discoveries of Vesalius and Harvey and their schools, the teachings of Galen received their death blow.

William Harvey was born in Folkstone, England, the son of a prosperous Kentish farmer. He studied at Cambridge and then at Padua, in Italy, as a pupil of Fabricius and Casserius. Unlike Vesalius, who published his monumental work at the age of twenty-eight, Harvey delayed publication of his great classic, "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus" (An Anatomical Disquisition on the Movement of the Heart and Blood in Animals), until 1628, when he was fifty years of age, and twelve years

after he had first begun lecturing on his revolutionary ideas. The opening paragraph of his dedication to Doctor Argent, President of the Royal College of Physicians, reads: "I have already and repeatedly presented you, my learned friends, with my new views of the motion and function of the heart, in my anatomical lectures; but having now for nine years and more confirmed these views by multiplied demonstrations in your presence, illustrated them by arguments, and freed them from the objections of the most learned and skilful anatomists, I at length yield to the requests, I might say entreaties, of many, and here present them for general consideration in this treatise."[46] In the introduction to his treatise he calls attention to the many errors and inconsistencies of the Galenical theory, and bravely states that wise men must learn anatomy, "not from the decrees of philosophers, but from the fabric of nature herself." In Chapter I, entitled "The Author's Reasons for Writing," Harvey says: "When I first tried animal experimentation for the purpose of discovering the motions and functions of the heart by actual inspection and not by other peoples books, I found it so truly difficult that I almost believed with Fracastorius, that the motion of the heart was to be understood by God alone . . . Finally, using greater care every day, with very frequent experimentation, observing a



William Harvey.
(1578–1657)

variety of animals, and comparing many observations, I felt my way out of this labyrinth, and gained accurate information, which I desired, of the motions and functions of the heart and arteries." Then, in the body of his work, based upon animal experiments, he proceeds to give an almost faultless solution of the fundamental physiological problem of the circulation of the blood, a solution which lacked completeness in only one particular, namely, the discovery of the capillary channels. Harvey, with his weak magnifying glasses, described all there was for him to see, and it was not until 1661, four years after Harvey's death, that the newly invented microscope revealed to Malpighi's eyes the microscopic channels through which the blood passes from the arteries to the veins.[47]

What Harvey actually proved can be recapitulated in the following manner: (1) that the ventricles of the heart are distinct muscular sacs which propel the blood that they contain into the aorta and pulmonary artery; that it is the contraction of the heart, and not its dilation, which coincides with the pulse; (2) that there are no pores in the septum of the heart, as had been contended by Galen, but that there is a complete circulation of the blood, i.e. the whole blood in the right ventricle is sent through the pulmonary artery to the lungs, is returned by the pul-

monary veins to the left auricle and thence flows into the left ventricle; that the whole blood in the left ventricle is again sent through the arteries to the tissues, then round by the smaller veins into the venae cavae, and by them to the right ventricle again; (3) that the arteries and veins contain not air or ethereal spirit, as had been maintained from the time of Galen, but blood; that the blood on the right side of the heart, though mixed with air, is still blood; (4) that most of the blood supplied to the tissues by the arteries runs through into the veins, and (5) that the heart, and not the liver, is the dynamical starting point of the blood.

Pioneer Microscopists. The seventeenth century, which gave to the scientific world Harvey's profoundly important demonstration of the circulation of the blood, also witnessed the rise of the pioneer microscopists. Although, as we shall see, Harvey's discovery brought about a more immediate change in the habits of medical thought and in the concepts of the nature of disease processes, yet the microscopists of the seventeenth century, by enlarging man's vision, prepared the soil out of which sprang the epochal microscopical discoveries of the nineteenth century. Just as Galileo, a contemporary of Harvey, with his telescope widened man's vision of the infinite starry vast of the sky, so did the pioneer microscopists give man a

glimpse into the hitherto invisible world of the infinitely small.

Kircher. Apparently, the earliest of the microscopists was the Jesuit priest, Athanasius Kircher (1602–1680) of Fulda, who is considered by some authorities to have been the first to employ the microscope in investigating the causes of disease. He employed a 32-power microscope and in his "Scrutinium pestis," published in Rome in 1658, he details experiments which he performed upon the nature of putrefaction. He showed how maggots and worms develop in decaying material and described countless broods of "worms" in the blood of plague patients, which he claimed were invisible to the naked eye, but could be seen with the aid of his microscope. Whether these "worms" which Kircher saw in plague blood were red blood cells or white blood cells[48] or even perhaps large secondary invading worms or maggots, is difficult to say, but it does seem rather improbable that, with a 32-power microscope, he could have actually seen plague bacilli. Regardless of this, Kircher would appear to have been the first to state explicitly the doctrine of a *contagio animata* as the cause of contagious disease.

Following Kircher, the pioneer microscopists were Hooke and Grew in England, Malpighi in Italy, and Swammerdam and van Leeuwenhoek in Holland.

Hooke and Grew. Robert Hooke (1635–1703) was a mechanical genius, who, among other things, invented a rather complicated compound microscope; in addition, it is probable that Hooke's "Micrographia," published in London in 1665, helped to inspire Nehemiah Grew's studies on the microscopic structure of plants, which are contained in his treatise "Idea of a Philosophical History of Plants" (1673) and "Anatomy of Vegetables" (1682).

Of more far-reaching importance was the work of Malpighi and Swammerdam and van Leeuwenhoek.

Malpighi (1628–1694), the founder of histology and the father of descriptive embryology, is noteworthy for the monumental discoveries he made serenely and gently under the lash of caustic criticism and even persecution.

He appeared at an epoch when such giants as Vesalius and Harvey had overthrown the universal confidence in the authority of the ancients, a period when there was suddenly work to do with no appeal to precedent, when the microscope suddenly threw open the enormous field of the minute and invisible, to the searching eye. Letters had fallen to a low ebb, ignorance was vast and overwhelming, and despite the brilliance of the preceding centuries, writers were given over to bombastic ornamentation of their writing, but a few honest and bold spirits turned from authority to nature, exact science arose. (Mac Callum)[49]

In 1661, in his greatest book "De Pulmonibus," he demonstrated the structure of the lungs, in which he stated that they were composed of lobules, intercommunicating with the trachea, and surrounded by a vascular network; he also formulated a tolerably correct conception of how the air and blood are brought together in the lungs. In 1660, he described the capillaries and recorded, for the first time, the actual observation of the passage of blood through the capillaries of the lung and the mesentery of the frog. The Malpighian, or deeper layer of the skin, which he was the first to describe, as well as the Malpighian bodies, which are lymphoid structures of the kidney and spleen, are immortal verbal testimonies to his anatomical contributions, described in his "De Viscerum Structura," Bonn, 1666; while his "De Formatione Pulli in Ovo" (1673) and "De Ovo Incubato" (1673) entitle him to the title of "the father of descriptive embryology."

Jan Swammerdam (1637–1680) was the first to see and describe the red blood corpuscles (1658); in 1664 he discovered, by the use of slender glass tubes, the valves of the lymphatic vessels, and in 1677 he devised the method of injecting blood vessels with wax, by means of which he was able not alone to follow blood vessels to their finer ramifications, but to study their valves, as well. He also definitely

opposed the current idea of the spontaneous formation of life.

Leeuwenhoek (1632–1723). And now we come to a contemporary of Malpighi and Swammerdam, a pioneer microscopist of the seventeenth century who, among his other bids to fame, was the first to see and accurately describe bacteria. Anton van Leeuwenhoek was born in Delft, Holland, the son of a family of well-to-do brewers. His schooling ended at sixteen, at which time he became bookkeeper and cashier in a clothing establishment in Amsterdam.[50] A few years later he returned to Delft, and married at the age of twenty-two. The remainder of his life was devoted to the study of natural history. His first publication referring to microscopic objects did not appear until 1673, when he was forty-one years old.

From the standpoint of bacteriology, which in the nineteenth century was to effect such a radical alteration in man's concepts of disease processes, the unique importance of van Leeuwenhoek lies in the fact that he was the first to see and accurately describe bacteria. In a letter to The Royal Society of London, dated September 17, 1683[51] (incidentally, van Leeuwenhoek was a most industrious letter writer; the number of letters, actually his scientific writings, which he sent to The Royal Society of London alone was 375) he thus delightfully records his microscopic obser-

vations upon some tartar which he scraped from his teeth:

Though my teeth are kept usually very clean, nevertheless when I view them with a Magnifying Glass, I find growing between them a little white matter as thick as wetted flower: in this substance though I could not perceive any motion, I judge there might probably be living Creatures.

I therefore took some of this flower and mixt it either with pure rain water wherein

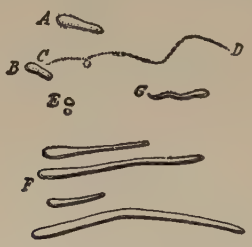


FIG. 9. First pictorial representation of bacteria. Leeuwenhoek, 1683.

were no animals; or else with some of my Spittle (having no Air bubbles to cause a motion in it) and then to my great surprise perceived that the aforesaid matter contained very many small living Animals, which moved themselves very extravagantly. The biggest sort had the shape of A (see Fig. 1), their motion was strong and nimble, and they darted themselves thro' the water or spittle, as a Jack or Pike darts thro the water. These were generally not many in number. The 2nd sort had the shape of B; these spun about like a top, and took a course sometimes on one side, as is shown at C and D; they were more in number

than the first. In the 3rd sort I could not well distinguish the Figure, for sometimes it seemed to be an Oval, and other times a Circle. These were so small that they seem'd no bigger than E and therewithal so swift, that I can compare them to nothing better than a swarm of Flies or Gnats, flying and turning among one another in a small space. Of this sort I believe there might be many thousands in a quantity of water no bigger than a sand, tho the flower were but the 9th part of the water or spittle containing it.

Besides these Animals there were a great quantity of streaks or threds of different lengths, but like thickness, lying confusedly together, some bent, and some straight as at F. These had no motion or life in them, for I well observed them, having formerly seen live-Animals in water of the same figure.

Leeuwenhoek extended his observations to others: two women; a child of eight years; the spittle of an "old Man that had lived soberly;" and another old man who was "a good fellow." The substance upon and between the teeth of the old men "had a great many living Creatures, swimming nimbler than I had hitherto seen":

The biggest sort were numerous, and as they moved, bent themselves like G. The other sorts of Animals were in great numbers, insomuch that tho the meal were little, yet the water that it was mixt with seemed to be all alive; there were also the long threads above mentioned.

In addition to his unique distinction of being the first man to see and accurately describe bacteria, van Leeuwenhoek has other signal discoveries to his credit. He was the first to describe the spermatozoa (1674), though Roger Bacon approached it, as evidenced by the Voynich Manuscript[52]; he gave the first complete description of red blood cells (1674); he was the first to see and describe parasitic protozoa (1674) and entozoic protozoa (Giardia) in 1681. According to Nuttall,[53] it was van Leeuwenhoek's observation that the flea may be attacked by a mite which gave rise to the well-known lines of Swift (1667–1745):

> So, naturalists observe, a flea
> Has smaller fleas that on him prey;
> And these have smaller still to bite 'em,
> And so proceed, ad infinitum.

He also was the first completely to demonstrate the capillary connection between arteries and veins, thereby forging the final link in the chain of Harvey's discovery of the circulation of the blood. Read what he wrote upon examining the tail of a tadpole under his microscope:

> A sight presented itself more delightful than any mine eyes had ever beheld; for here I discovered more than fifty circulations of the blood in different places, while the animal lay quiet in the water, and I could bring it before my microscope to my wish. For I saw not

only that in many places the blood was conveyed through exceedingly minute vessels, from the middle of the tail toward the edges, but that each of the vessels had a curve or turning, and carried the blood back toward the middle of the tail, in order to be again conveyed to the heart. Hereby it plainly appeared to me that the blood-vessels which I now saw in the animal, and which bear the names of arteries and veins are, in fact, one and the same; that is to say, that they are properly termed arteries so long as they convey the blood to the furthest extremities of its vessels, and veins when they bring it back to the heart. And thus it appears that an artery and a vein are one and the same vessel prolonged and extended.

He was also the discoverer of the branched character of heart muscle, of the stripe in voluntary muscle, and of the structure of the crystalline lens.

What was the nature of the microscopic paraphernalia which this wizard of the seventeenth century possessed? In his hands, the simple microscope and simple lenses received their highest development. He manufactured and ground lenses with diamond dust and fastened them himself to stages. He manufactured and owned 419 lenses and 247 microscopes, a few of which he presented to the Royal Society of London, where they are still to be seen. Charles Singer, who has tested these instruments, says that their highest magnification is about 160 diameters Other

simple microscopes which van Leeuwenhoek made magnified from 40 to 133 diameters.

Rise of the Theoretical Systematists. Harvey's demonstration of the circulation of the blood, published in 1628, and the development of mathematics and physical sciences, brought about a fundamental change in the habits of medical thought during the latter half of the seventeenth century, as well as through the eighteenth century. In the wake of Harvey's discovery, which showed that many of the vital processes of the human body are explainable by the ordinary laws of mechanics, there arose schools or systems of medical theorists which attempted to explain disease, and to establish medicine, on a physiological or mechanical basis. All of these theoretical systematists, handicapped by the incomplete scientific knowledge of their times and by their tendency to stress one explanation of bodily processes in health and disease to the exclusion of all others, founded schools of medical thought which have failed to survive. Historically, however, they represent the courageous, though often misguided, attempt to explain bodily behavior, normal and abnormal, in terms of mechanics, physics and chemistry. Before considering these schools of thought, we would pause to take up an eccentric mystic systematist of the early part of the seventeenth century, Van Helmont.

J. B. van Helmont (1578–1644) was a highly educated Belgian of noble family; he has been termed the "Descartes of Medicine."[54] The theory which he advanced to explain disease actually represented the ideas of Paracelsus, dressed in somewhat more complicated and fantastic trappings. Van Helmont taught that disease arose from a conflict between the Archaeus, or spirit of life, situated in the stomach, and the secondary Archaeus in the kidneys and liver; over both was supposed to preside the vital principle, which resided in the stomach and spleen. Health resulted when the body was ruled by a happy and contented Archaeus; disease arose when the Archaeus, or ruling spirit, became disturbed. Fever arose from injury done to the Archaeus by the cause of the fever; the period of chills was an expression of the Archaeus' terror or passion; and the heat an expression of its fury. Van Helmont, a believer in the doctrine of animism, considered disease to be something active, and not a mere impairment of health; among the occasional causes of disease he listed demons, witches, ghosts and necromancers. Van Helmont is also of interest because he based his system of physiology on the theory of fermentations. He taught that the food absorbed from the intestines becomes endowed with natural spirits in the liver; then, in the heart, the natural

spirits are converted into vital spirits, and in the brain the vital spirits become animal spirits. He took issue with Paracelsus, who claimed that the three elements are sulphur, mercury and salts, and contended that there are only two elements, air (the natural atmosphere) and water; but he largely followed, in his system, the main outlines of Paracelsus' chemical theories.

Sylvius and the Iatrochemical School. Sylvius (1614–1672), sometimes referred to by his full name Franciscus de la Boe, was a member of a French family settled in Holland. He was professor of medicine at Leyden for fourteen years, and his lectures and clinics caused students to flock to him from all over Europe. To Sylvius is due the introduction of modern clinical teaching (Osler[55]). In 1664, he wrote: "I have led my pupils by the hand to medical practice, using a method unknown at Leyden, or perhaps elsewhere, i.e. taking them daily to visit the sick at the public hospital. There I have put the symptoms of disease before their eyes; have let them hear the complaints of the patients, and have asked them their opinions as to the causes and rational treatment of each case, and the reasons for those opinions. Then I have given my own judgement on every point. Together with me they have seen the happy results of treatment when God has granted to our cares a restoration of

health; or they have assisted in examining the body when the patient has paid the inevitable tribute to death." He was the founder of the so-called Iatrochemical School, which really represented a premature but honest attempt on the part of Sylvius to explain disease on the basis of the new chemical concepts, as well as upon the new doctrine of the circulation of the blood. The doctrines of Sylvius attained widespread acceptance in Holland and Germany, particularly.

The system which Sylvius proposed was based essentially upon the Hippocratic idea of humors. However, instead of the four cardinal humors of Hippocrates, Sylvius adopted a triumvirate, the saliva, the pancreatic fluid, and the bile. For the "forces" he substituted fermentation and effervescence; for the "qualities" acid and alkali, originating in the acid or alkaline salt. Saliva and pancreatic fluid, Sylvius taught, are acid; bile is alkaline. Health consists in the undisturbed performance, in the body, of fermentation, without the appearance of the acid or alkaline salt. If, however, one of these latter salts becomes prominent, it gives rise to an "acridity" and furnishes the cause of disease.

He divided all diseases into two groups: (1) those depending upon an acid "acridity" and (2) those originating in an alkaline "acridity." Numerous modifications of the

two varieties of acridity may occur, and hence arise subordinate classes of the two main groups of diseases. Sylvius' therapy consisted in the administration of alkali to remove the acid, or of acid to remove the alkali. An idea of his line of reasoning can be gained from the following quotation from his writings:

As often as the whole blood appears black, it indicates that acidity predominates; if the blood is redder, it shows that the bile in it is superabundant. In the first case, that acid in the blood must be diminished; in the second the bile must be lessened and its power broken. If the blood, which normally is free from odor and of a sweetish taste (especially the serum), tastes salty, the alkali in the body is too pure, and when brought into contact with the acid spiritus engenders a humor of a saline taste and prejudicial to the body; for such a taste, though milder, may pass into the urine, but not into the serum or its products, the lymph, the pancreatic juice and the saliva. This saline taste indicates a reduction and correction of the alkali.

Borelli and the Iatrophysical School. Opposed to the Iatrochemical School which did stand in rather close relation to practical medicine, G. A. Borelli (1608–1679) founded the Iatrophysical School. The keynote of Borelli's teaching was that all of the phenomena of health and disease can be reduced to physical and mechanical processes. Bone and muscle movements

were explained on the lever theory; digestion was looked upon as being essentially a process of mechanical trituration, or grinding. Not alone in physiology, but into the domain of pathology as well, the school of Borelli entered, and disease, and its various symptoms, were explained on a mechanical basis.

Progress in Clinical Observation. In striking contrast to these opposing schools of medical thought, there arose in England during the seventeenth century Thomas Sydenham, who refused to become a partisan of any school and who exerted a pronounced influence by his insistence that scientists leave by their theorizing until more facts had been ascertained by careful, painstaking clinical observation of disease phenomena.

Sydenham (1624–1689). A contemporary of van Leeuwenhoek, Thomas Sydenham, in England, marked an epoch by his clinical descriptions and observations, particularly of hysteria, gout, scarlet fever, and the form of chorea still known by his name. He was a rebel and an iconoclast, who took his degree in Medicine at Cambridge in 1676, and has been called the "English Hippocrates" because he, more than any other man, revived the Hippocratic tradition in medicine. When once asked as to the best authors to read for acquiring knowledge of medical practice, he told his inquirer to read Don Quixote.

John Locke, the famous philosopher and physician, was a close friend and associate of Sydenham. In a letter to William Molyneux, Locke thus referred to the practical side of Sydenham's medical teachings: "You cannot imagine how far a little observation carefully made by a man not tied up to the four humours [Galen], or sal, sulphur and mercury [Paracelsus], or to acid and alcali [Sylvius and Willis] which has of late prevailed, will carry a man in the curing of diseases though very stubborn and dangerous; and that with very little and common things, and almost no medicine at all."

Sydenham, whose influence on seventeenth century medicine was great, was an acute clinical observer unenslaved by theories in his practice, although he failed to rid himself of all the hypotheses of the Galenic School. As affording an insight into his general method of approach to the phenomena of disease, the following extract from the dedication of his treatise "Medical Observations on the History and Cure of Acute Diseases" is representative of his common sense:

> The only means of acquiring a correct knowledge of the fundamental principles of medicine consists in attentive observation of the whole of the phenomena of disease, and vigilant and minute inquiry into the progress and fluctuations of the several symptoms, from which alone the true and natural indications of cure can be deduced.

And in the opening paragraphs of the same treatise, Sydenham reiterates the Hippocratic definition of disease:

A disease, in my opinion, how prejudicial soever its causes may be to the body, is no more than a vigorous effort of Nature to throw off the morbific matter, and thus recover the body. For as God has been pleased so to create mankind, that they should be fitted to receive various impressions from without, they could not, upon this account, but be liable to different disorders; which arise (1) either from such particles of the air, as having a disagreement with the juices, insinuate themselves into the body, for want of its being able to digest, and discharge them, on account of their too large bulk, or unsuitable nature . . . These circumstances being so closely interwoven with our constitutions that no man can be entirely free from them, Nature provides such a method, and train of symptoms, as may expel the peccant matter that would otherwise destroy the human fabric.

Of value in giving an insight into the curiously chaotic ideas concerning the nature of disease held by one of the most acute medical observers of the seventeenth century, the following quotations from Sydenham's writings are of interest: "Acute diseases come from God, but chronical diseases originate with ourselves." Although Sydenham writes of smallpox as "infecting whole families and sparing none, of what age soever they be, if they have not had this disease already,"

he goes on to say: "I ingenuously acknowledge, that by reason of a defect in the understanding which is common to me and the rest of mankind, I know not the essence of this disease." On another page he reveals his real view, which is Galenical in origin; "the constitution of the air being not so inclinable to produce the Bloody-Flux gave occasion to the Small Pox." Sydenham, himself, regarded his work as merely an initial stage in the description of diseases. "I am like a grindstone," he once said, "which, without itself being able to cut, yet continually whets the iron."

The stress which Sydenham laid upon the influence of season and climate on infectious diseases has led certain writers to characterize Sydenham as "the first great epidemiologist."[56] As Major Greenwood[57] points out, Sydenham's three great contributions to epidemiology were (1) his insistence that each specific disease undergoes a definite evolutionary cycle, rising, declining and falling; he predicted that diseases such as smallpox and leprosy would run their natural course and be succeeded by other diseases. (2) he was the first to familiarize the profession with the influence of meteorological conditions upon the prevalence of epidemic diseases, and (3) his theory of epidemic constitutions, which amounted to this: "Although different acute diseases are specific in origin,

they tend to vary in their clinical manifestations from time to time, and to vary together; the common type changes, but different specific forms converge towards the fashionable type; much as specifically distinct butterflies and moths come to resemble externally a common form (mimicry)." Payne[58] summarizes Sydenham's contribution in a peculiarly apt manner:

> His great merit was to proclaim the great truth that science was, is, and always must be incomplete; and that danger lurks in the natural tendency to act upon it as if it were complete. The practical man has to be guided not only by positive knowledge, but by much that is imperfectly known. He must listen to the hints of Nature as well as to her clear utterances.

Sydenham was not alone, among seventeenth century physicians, in devoting close attention to the natural history of disease. Tobias Cober (1606) noted the relation between typhus fever and pediculosis; Spieghel (1624) wrote an extensive account of malarial fever: Daniel Sennert, in 1624, published a treatise on scurvy and in 1626, a treatise on dysentery, as well as a treatise on the heart. Arnold de Boot, a Frisian practicing in Ireland, described in 1649 rickets, a hitherto undescribed disease, and Francis Glisson, in 1650, still further extended de Boot's observations. Isbrand de Diemerbroek, in his "De Peste" (1646) carefully described bubonic plague

and, in 1665 the first autopsy upon a plague victim appears to have been performed by Nathaniel Hodges, of London.

Willis (1621–75). An English clinical contemporary of Sydenham was Thomas Willis, whose "Cerebri Anatome," (1664) was the most advanced treatise upon the nervous system that had yet appeared. In his "De Febribus," published in London in 1659, Willis gave the first account of epidemic typhoid fever, based upon the disease as it manifested itself among the troops of the Parliamentary Wars (1643). In the same treatise, Willis first named and described puerperal fever.

The Doctrine of Spontaneous Generation. The belief in spontaneous generation, or the doctrine of abiogenesis, was widely held in ancient times and throughout the Middle Ages. It postulated that living things are spontaneously generated from non-living material. The Bible and Aristotle record the widespread prevalence of this belief. Pliny (23–79 A.D.) speaks of frogs and mice begot of the mud of the river Nile. The dew was thought to give rise to insects. Bees generated from the flesh of lions were thought to be stronger and more courageous than those sprung from the flesh of bullocks. Van Helmont, in the sixteenth century, gave a celebrated recipe for creating mice; all that is required is to place some dirty linen in a

receptacle, along with a few grains of wheat or a piece of cheese. And somewhat later an Italian, Buonanni, announced that certain timber-wood after rotting in the sea, produced worms, which in turn engendered butterflies, and these butterflies, in turn, became birds. Even as late as the seventeenth century, when Sir Thomas Brown expressed doubt that mice are bred by putrefaction, the English naturalist Alexander Ross replied:

> So may we doubt whether in cheese and timber worms are generated, or if beetles and wasps in cow-dung, or if butter-flies, locusts, shell-fish, snails, eels, and such life be procreated of putrified matter, which is to receive the form of that creature to which it is by formative power disposed. To question this is to question reason, sense, and experience. If he doubts this, let him go to Egypt, and there he will find the fields swarming with mice begot of Nylus, to the great calamity of the inhabitants.

Redi. It is a strange fact that it was not until the year 1668 that the doctrine of spontaneous generation was subjected to its first experimental test. The man to whom credit is due for this epoch-making venture was Francesco Redi (1626–1697), an Italian physician living in Arentino. Medical adviser to two of the grand dukes of Tuscany, poet, (his best known poem "Bacco in Tuscana" is in praise of the various Tuscan wines), linguist, naturalist,

as well as physician, his collected works, embracing nine volumes, one of which was of sonnets, were published in Milan in 1809–1811.

In addition to his monumental demonstration of the falsity of the doctrine of the spontaneous generation of visible plants and animals, Redi was the first to demonstrate ascaris eggs and the first to demonstrate the reproductive organs in the ascaris of man. In his monograph entitled "Osservaziono Intorno agli Animali Viventi che si trovano negli animali viventi" (1684), he described 108 different species of parasites, of man and various animals, belonging to the cestodes, trematodes, nematodes, insects, etc., a work which has earned him the title of "the father of parasitology." In commenting on the fact that he was unable to find pediculi on lions and tigers he naively noted: "The search for parasites on these animals is attended with considerable difficulty."

The volume in which Redi recorded his experiments on spontaneous generation was published in quarto form in Florence in 1668, and was entitled "Esperienze Intorno alla Generazione degl' Insetti" (Experience Met with in the Generation of Insects). In twenty years five editions of this work had appeared. Simple and homely were these experiments, directed specifically against the prevailing belief, held for thousands of years, that maggots

were spontaneously generated in decaying meat. He placed meat in a series of wide-mouthed flasks or jars; some he left freely open to the air; others he covered with paper; and the remainder he covered with a fine Neapolitan veil. In all these vessels, the meat decayed, and flies were attracted by the smell. He watched the flies crawl down into the open vessels, when they deposited their eggs on the putrid meat, and soon from the eggs came a large crop of maggots; and later from the maggots developed new flies. The meat in the covered flasks likewise decayed, but no maggots developed in the meat; however on top of the veil which covered certain of the flasks, high above the decaying meat, flies laid their eggs, and then the hatched maggots appeared on the surface of the veil, but not in the meat or within the vessel.

From these very simple experiments, and their profoundly important implication that the experimental method is the most efficient means of learning the truth concerning biological phenomena, Redi drew the perfectly valid conclusion that maggots arise in decaying meat from the hatching of eggs of flies, and not by spontaneous generation. In Redi's own words:

> Although content to be corrected by anyone wiser than myself, if I should make erroneous statements, I shall express my belief that the Earth, after having brought forth the first

plants and animals at the beginning by order of the Supreme and Omnipotent Creator, has never since produced any kind of plants or animals, either perfect or imperfect; and everything which we know in past or present time she has produced, came solely from true seeds of the plants and animals themselves, which thus, through means of their own, preserve their species.[59]

Confirmation and extension of Redi's findings at the hands of Swammerdam (1637–1681) and Vallisnieri, (1661–1730) the latter being a medical professor in Padua, Italy, who showed that the grub in a fruit also arises from an egg laid by an insect before the fruit develops, served to explode the idea that forms of life visible to the naked eye are capable of spontaneous generation. But as so frequently happens, an erroneous, long-held doctrine, when driven from one corner, finds refuge in another which is less clearly lighted. A few years after Redi's experiments were published, van Leeuwenhoek, as we have already seen, discovered infusoria and then still minuter living forms, the bacteria. These microscopic microorganisms, hitherto unseen, represented the haven in which the adherents of the theory of spontaneous generation took refuge. "Granted," they said, "that Redi has forever disproven that animals and insects visible to the naked eye are not spontaneously generated! Microscopic organisms *are* spon-

taneously generated, and it is in them that are to be found the beginnings of life, the point where lifeless, inorganic matter is changed by natural agencies into organized, but microscopic life." And so the matter stood for seventy years, until the early part of the eighteenth century, when Needham entered the lists with what he claimed to be experimental proof of the spontaneous generation of microscopic animalcula.

Popular Seventeenth Century Ideas Regarding Disease. It is quite evident that the ideas held by scientists during the seventeenth century regarding the nature of disease were in a chaotic state. One school looked upon disease as an obstruction of the blood vessels and therefore recommended deobstruent remedies to dilute the blood. (In this connection Willis, one of the leading physicians of the seventeenth century, writing on inflammation of the lungs, said that he believed the essential cause to be: "that the blood boiled feverishly, and sticking within the more narrow passages of the lungs engendered there an obstruction, causing inflammation.") Another school taught that disease was explainable in terms of acidity, and therefore employed alkaline treatment. Others held to the theory of vitiated humors, and recommended removal of the "peccant humor" by the use of purgatives, diuretics, bloodletting and sweating, methods to

which the great Sydenham was partial. It is not strange that in this chaos of scientific thought the seventeenth century layman, whose knowledge always lags behind the advances of science, should have harbored conflicting and often bizzare notions concerning the diseases which afflicted him.

Molière's satirical picture of a physician illustrates one phase of the situation in his time (1622–1673):

> Above everything, that which pleases me in him, and in which he follows my example, is that he attaches himself blindly to the opinions of our fore-fathers, and that he has never chosen either to comprehend or to listen to the reasons and the experiments of those pretended discoveries of our age touching the circulation of the blood and other opinions of the same kidney.

In another place, Molière says: "My physician comes to see me and we talk together. He gives me advice. I neglect to follow it, and I get well."

The most graphic popular account of a great seventeenth century epidemic is to be found in Daniel Defoe's "A Journal of the Plague Year; being observations or memorials of the most remarkable occurrences, as well public as private, which happened in London during the last great visitation in 1665." After mentioning a comet which appeared shortly before the plague broke out, Defoe[60] writes:

The apprehensions of the people were likewise strangely increased by the error of the times, in which, I think, the people, from what principle I cannot imagine, were more addicted to prophecies and astrological conjurations, dreams, and old wives' tales than ever they were before or since.

But there was still another madness beyond all this, which may serve to give an idea of the distracted humour of the poor people at that time, and this was their following a worse sort of deceivers than any of these; for these petty thieves only deluded them to pick their pockets and get their money, in which their wickedness, whatever it was, lay chiefly on the side of the deceivers deceiving, not upon the deceived. But in this part I am going to mention it lay chiefly in the people deceived, or equally in both, and this was in wearing charms, philtres, exorcisms, amulets, and I know not what preparations, to fortify the body with them against the plague; as if the plague was not the hand of God, but a kind of a possession of an evil spirit, and that it was to be kept off with crossings, signs of the zodiac, papers tied up with so many knots, and certain figures or words written on them, as particularly the word Abracadabra, formed in triangle or pyramid.

A particularly good exposition of the chaotic ideas in regard to disease is to be found in the following quotation, also from Defoe's Journal:[61]

This put it out of question to me, that the calamity was spread by infection; that is to say, by some certain steams or fumes, which

the physicians call effluvia, by the breath, or by the sweat, or by the stench of the sores of the sick persons, or some other way, perhaps, beyond even the reach of the physicians themselves, which effluvia affected the sound who came within certain distance of the sick, immediately penetrating the vital parts of the said sound persons, putting their blood into an immediate ferment, and agitating their spirits to that degree which it was found they were agitated; and so those newly infected persons communicated it in the same manner to others. And this I shall give some instances of, that cannot but convince those who seriously consider it; and I cannot but with some wonder find some people, now the contagion is over, talk of its being an immediate stroke from Heaven, without the agency of means, having commission to strike this and that particular person, and none other, which I look upon with contempt as the effect of manifest ignorance and enthusiasm; likewise the opinion of others, who talk of infection being carried on by the air only, by carrying with it vast numbers of insects and visible creatures, who enter into the body with the breath, or even at the pores with the air, and there generate or emit most acute poisons, or poisonous ovae or eggs, which mingle themselves with the blood, and so infect the body; a discourse full of learned simplicity, and manifested to be so by universal experience; but I shall say more to this case in its order.

Le Sage's "Gil Blas," that immortal work of historical fancy, was published in 1715, but it is generally considered to be a

faithful, if somewhat exaggerated, mirror of seventeenth century Spain. Upon being apprenticed to Doctor Sangrado, who "had more practice than any physician of his time in Valladolid," Gil Blas thus records that medical worthies' advice to him:

Remember, my friend, that bleeding and drinking warm water are the two grand principles; the true secret of curing all the distempers incident to humanity. Yes, this marvelous secret which I reveal to you, and which nature, beyond the reach of my colleagues, has failed in rescuing from my pen, is comprehended in these two articles—namely, bleeding and drenching. Here you have the sum total of my philosophy; you are thoroughly bottomed in medicine, and may raise yourself to the summit of fame on the shoulders of my long experience. (Book II, Chap. III).

Elsewhere, we find:

The smallpox and a malignant fever [plague] took alternate possession of the town and the suburbs. All the physicians in Valladolid had their share of business, and we not the least. We saw eight or ten patients a day; so that the kettle was kept on the simmer, and the blood in the act of transpiring. But things will happen cross; they died to a man, either by our fault or their own. If their case was hopeless, we were not to blame; and if it was not hopeless, they were. Three visits to a patient was the length of our tether. About the second, we sometimes ran foul of the undertaker; or when we had been more

fortunate than usual, the patient had got no further than the point of death. As I was but a young physician, not yet hardened to the trade of an assassin, I grieved over the melancholy issue of my own theory and practice. Sir, said I, one evening to Doctor Sangrado, I call heaven to witness on the spot that I have never strayed from your infallible method; and yet I have never saved a patient: one would think they died out of spite, and were on the other side of the great medical question. This very day I came across two of them, going into the country to be buried. My good lad, replied he, my experience nearly comes to the same point. It is but seldom I have the pleasure of curing my kind and partial friends. If I had less confidence in my principles, I should think my prescriptions had set their faces against the work they were intended to perform. If you will take a hint, sir, replied I, we had better vary our system. Let us give, by way of experiment, chemical preparations to our patients; the worst they can do is to tread in the steps of our pure dilutions and our phlebotomizing evacuations. I would willingly give it a trial, rejoined he, if it were a matter of indifference, but I have published on the practice of bleeding and the use of drenches: would you have me cut the throat of my own fame as an author! Oh! you are in the right, resumed I; our enemies must not gain this triumph over us; they would say that you were out of conceit with your own systems, and would ruin your reputation for consistency. Perish the people, perish rather our nobility and clergy! But let us go in the old path. After all, our brethern of the faculty,

with all their tenderness about bleeding, have no patent for longevity any more than ourselves; and we may set off their drugs against our specifics.

THE EIGHTEENTH CENTURY

Spallanzani and Spontaneous Generation. We have seen how the seventeenth century was torn with dissension over the question of spontaneous generation. Throughout the eighteenth century the controversy waged, and here we find the two outstanding antagonists to be Needham and Spallanzani.

Needham (1713–1784) was an Englishman, and a Catholic priest residing on the Continent, who was for many years Director of the Academy of Maria Theresa at Brussels. He became a friend of Buffon (1707–1788), the French naturalist, with whom he performed and published many of his experiments. The results of Needham's experiments were first published in 1748. He announced that he had taken some meat extract, obtained by boiling meat in water, as well as vegetable infusions of seeds and almonds, into flasks or vials which he then carefully corked with porous cork stoppers, and sealed with mastic. He then heated these flasks for a short time by immersing them in boiling water, and in hot ashes. After the flasks had cooled, he set them aside at room temperature for several days, when lo and behold he

Lazzaro Spallanzani.
(1729–1799)

found his sealed flasks to be literally teeming with animalcules, when he examined a drop of their contents under a microscope. Inasmuch as Needham was convinced that the heating had killed all the germs that may have been present in the flasks, he victoriously announced that the living forms which developed in the flasks had been produced by spontaneous generation. In addition, Needham promulgated an explanation of the spontaneous generation of life, which Buffon later elaborated into a system which became quite the social rage at the French Court. Needham said that the thing which caused little animals to appear in his heated infusions was a force, the vegetative or productive force; and this force has the function of forming the organic world. Buffon still further elaborated this idea. Animals and vegetables, he said, possess certain primitive, deathless parts, or organic molecules, in common. These organic molecules cast themselves into the moulds or shapes which constitute different living beings. When a living thing, be it animal or plant, is destroyed by death, the immortal, ever active organic molecules become liberated. Thereupon they become active in the putrified material, appropriate to themselves some raw particles and form, writes Buffon, "by their reunion, a multitude of little organized bodies, of which some, like earthworms, and fungi, seem to be

fair-sized animals or vegetables, but of which others, in almost infinite numbers, can only be seen through the microscope." Not alone fair-sized animals and vegetables, such as earthworms and fungi and also microscopic animalcules did he believe arose and existed only through spontaneous generation, but intestinal worms as well. And he adds: "The eels in flour paste, those of vinegar, all those so-called microscopic animals, are but different shapes taken spontaneously, according to circumstances, by that ever active matter which only tends to organization."

Now enters into the experimental lists a fellow-countryman of Redi, Lazzaro Spallanzani (1729–1799), a man educated for the Catholic Church (and hence usually known as Abbé Spallanzani), but whose love of natural science and experimentation led him into research and teaching. In addition to his studies on spontaneous generation, his scientific contributions to the physiology of fertilization, of digestion, and of respiration were of far-reaching import. Of his studies on gastric digestion, Beaumont wrote:[62]

> Suffice it to say, that the theories of concoction, putrefaction, trituration, fermentation and maceration have been prostrated in the dust before the lights of science and the deductions of experiment. It was reserved for Spallanzani to overthrow all these unfounded hypotheses, and to erect upon their ruins a

theory which will stand the test of scientific examination and experiment. He established a theory of chemical solution, and taught that chymification was owing to the solvent action of a fluid, secreted by the stomach, and operating as a true menstrum of alimentary substances. To this fluid he gave the name of gastric juice.

First a professor at Bologna, he later was called to a professorship at the University of Pavia, in Lombardy.

Spallanzani suspected the precision with which Needham's experiments had been performed; he suspected that Needham had not subjected his flasks to a sufficient degree of heat to kill the contained animalcula; for Needham had not recorded the degree of temperature, nor the length of time, to which his flasks had been subjected. Moreover, he suspected the porous stoppers which Needham had used for sealing his flasks, stoppers which, he suspected, might perhaps have allowed the ingress of outside microorganisms. First, Spallanzani introduced an important technical innovation in the experimental study of this question of the spontaneous generation of life, by employing glass flasks with slender necks which he hermetically sealed after the nutrient liquids, juices of meats and vegetables, had been introduced into the flasks.

Let Spallanzani describe the results of his experiments in his own words:

I repeated that experiment with more accuracy. I used hermetically sealed vases. I kept them for an hour in boiling water, and after having opened them and examined their contents within a reasonable time I found not the slightest trace of animalculae, though I had examined with the microscope the infusions from nineteen different vases.

From these experiments Spallanzani drew the conclusion that living material, such as animalculae, always originate from other living material. The results of Spallanzani's experiments were published in 1775, one year before the outbreak of the American Revolution.

But Needham was not defeated. He retorted that by leaving his vases in boiling water for an hour, Spallanzani had not only destroyed the contained animalculae, but he had weakened, or perhaps killed, the germinative or "vegetative" force of the infusion itself, from which force Needham contended that animalculae are generated. He advised that Spallanzani try subjecting his vases to less heat.

It must be admitted that Spallanzani did not completely succeed in disproving Needham's arguments. He did, however, conclusively demonstrate that, no matter how long the infusions in the flasks were boiled, if now the infusions again were exposed to the air, animalculae appeared within a few days. In view of subsequent discoveries of bacterial spores, whose resis-

tance is such that they can withstand boiling water for several hours, it must be noted that there was perhaps an element of luck in the success of Spallanzani's experiments, possibly partly due to the purity of the air in which he worked.

Voltaire laughed at Needham and, for the amusement of his readers, called him an Irish Jesuit. In his "Philosophic Dictionary," he wrote: "It is very strange that men should deny a creator and yet attribute to themselves the power of creating eels." However, even as late as 1846, Ernest Bersot, who later became a director of the École Normale in France, wrote in his book Spiritualism:

> The doctrine of spontaneous generation pleases simplicity-loving minds; it leads them far beyond their own expectations. But it is yet only a private opinion; and, were it recognized, it would have to be limited and narrowed down to the production of a few inferior animals.

It is curious to find how one of the great scientific events of the eighteenth century, the discovery of oxygen by Priestley in 1774, influenced the hotly debated question of the spontaneous generation of life. For, now, the proponents of this theory said: "Since oxygen is necessary to all forms of life, had not the boiling of Spallanzani's sealed flasks changed the oxygen in such a manner that its life-giving prop-

erties had been destroyed?" And it is also of interest to note that it was not until 1860, and thereafter, that this ubiquitous specter of spontaneous generation was finally laid low by the epoch-making researches of Pasteur.

Plenciz and the Contagionum Vivum Theory of Disease. Van Leeuwenhoek, it will be remembered, died in 1723, but it was in 1683 that he announced his discovery of bacteria. It is of interest to note that an anatomist, Giovanni Maria Lancisi (1654–1720), the author of a classical work on diseases of the heart, published in the early part of the eighteenth century an essay entitled "Swamp Emanations and Their Cure" (1717). In this, he quite definitely traced the relation between swamp fevers and the mosquito, and considered the possibility, without adducing proof, of an infected insect causing, by its bite, "worms in the blood;" he suggested that the cure for swamp fevers lay in the drainage of swamps.

For years the possible relation of Van Leeuwenhoek's "animalcules" to disease remained unsuspected and it was not until 1762, seventy-nine years after Van Leeuwenhoek's discovery of bacteria and thirty-nine years after his death, that the possible significance of bacteria was first recognized. It was in 1762, then, that Plenciz, a Vienna physician, announced a more or less definite *contagium vivum* theory of the

causation of disease. Although the conclusions that he drew were not warranted by the experimental observations that he made, yet the fact remains that Plenciz held that each disease has its own living, specific, exciting agent which, upon entrance into the body, multiplies enormously and gives rise to the lesions and symptoms of that disease. He found animalcula in various sorts of decomposing materials, and, apparently he was the first to describe "the bread ferment." From Plenciz on, the *contagionum vivum* doctrine was bound up with theories of fermentation, decomposition and spontaneous generation. It is curious that in the seventeenth century Robert Boyle (1627–1691), the noted physicist, prophesied that the explanation of the causation of disease would be found in the explanation of fermentation. In his essay on the "Pathological Part of Physic" he wrote:

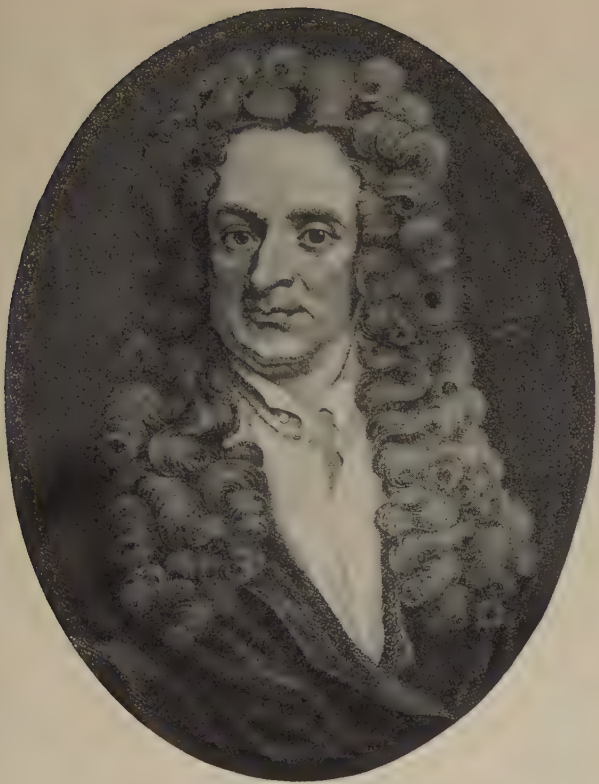
> And let me add that he, that thoroughly understands the nature of ferments and fermentation, shall probably be much better able than he that ignores them to give a fair account of divers phenomena of several diseases (as well as fevers and others) which will, perhaps, be never properly understood without an insight into the doctrine of fermentation.

However, so little was actually known about bacteria that Linnaeus, the founder of nomenclature in natural history, classified bacteria in 1758 in one group which he

called Chaos. A rather distinct advance in the knowledge of microorganisms is marked by the treatise of Otto Friedrich Müller, of Copenhagen, a work published in 1786 and entitled: "Animalcula Infusoria," a volume of 367 pages. Müller used, in his studies, a compound microscope, invented by the Janssens and improved by Fontana, which gave a magnification of 300 diameters. In this book not only did Müller have fifty plates of sketches of infusoria, but he attempted a crude classification and introduced such terms as "Proteus" and "Vibrio," which have retained to the present day much of their original significance.

FURTHER THEORETICAL SYSTEMATISTS

The Iatromathematicists. The endeavor, which began in the seventeenth century, to find complete theoretical systems which would explain health and disease was continued throughout the eighteenth century. As a continuation of the Iatrophysical School of the preceding century, as well as an attempt to apply Newton's (1642–1727) astronomical generalizations to the field of medicine, there arose in England a group of physicians who endeavored to reduce the phenomena of health and disease to mathematical terms and doctrines. Richard Mead (1673–1754), author of "Mechanical Account of Poisons" (1702) and "The Power of the Sun and Moon over



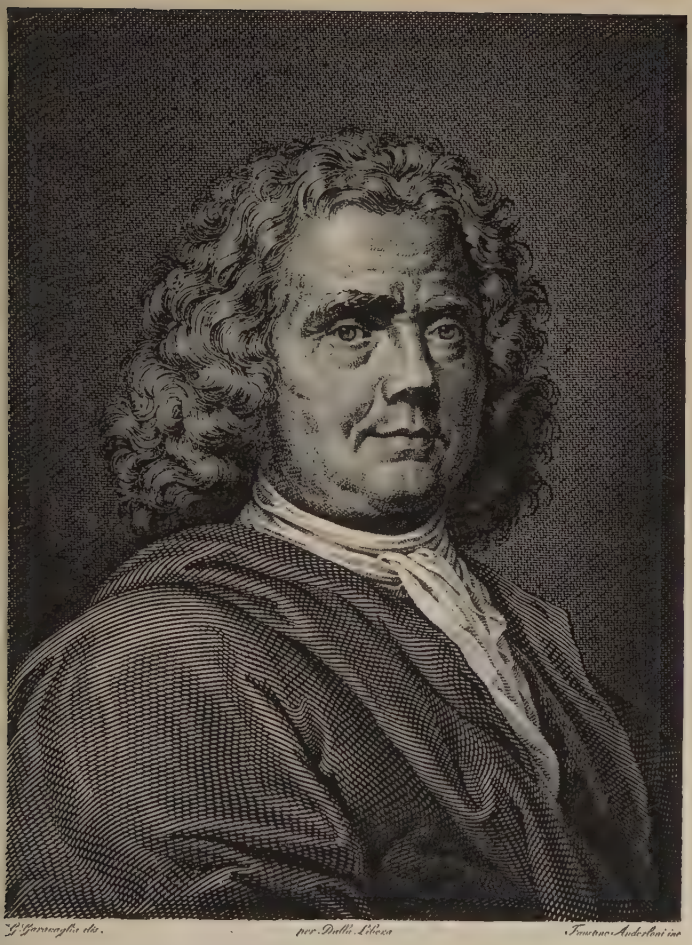
Sir Isaac Newton.
(1642–1727)

Human Bodies" (1704) was not only an eminently successful physician but a man of great learning. He wrote:

> It is very evident that all other means of improving medicine have been found ineffectual, by the stand it was at for two thousand years, and that, since mathematicians have set themselves to the study of it, men already begin to talk so intelligently and comprehensibly, even about abstruse matters, that it is to be hoped that mathematical learning will be the distinguishing mark of a physician and a quack.

In his treatise published in 1704, Mead endeavored to explain disease in terms of atmospheric pressure and by solar and lunar influences. Archibald Pitcairne (1652–1713), George Cheyne (1671–1743), John Freind (1675–1728) and William Cole (1635–1716) were distinguished English contemporaries who elaborated upon the teachings of the Italian Iastromechanical School of the seventeenth century. Their endeavor was to explain not only such physiological processes as menstruation by principles of mechanics, but the causation of fevers and the action of poisons as well.

Boerhaave. Hermann Boerhaave (1668–1738) is notable as being one of the greatest physicians of the eighteenth century and one of the great medical teachers of all time. Professor of medicine at Leyden, his fame was so wide that letters addressed



Hermann Boerhaave.
(1668–1738)

"Dr. Boerhaave, Europe" were laid upon his table, and the hospital of Leyden, with its mere dozen beds available for teaching purposes, became the center of medical influence in Europe. An avowed and enthusiastic disciple of the methods of Hippocrates and Sydenham, Boerhaave unceasingly stressed the importance of applying physiological, anatomical and microscopic discoveries to the practice of medicine, thereby becoming one of the pioneers in modern methods of clinical instruction.

In the ideas which he held as to the nature of disease processes, Boerhaave is generally regarded as belonging to the Iatromechanical School of Borelli, although he is said to have also taught the acid and alkaline acridity theory. He held that disease is a condition in which the bodily actions are disturbed, which takes place only with difficulty. Fever, he taught, is the effort of nature to ward off death.

Stahl and Hoffmann. George Stahl (1660–1734), a professor of medicine at Halle, elaborated an animistic theory of disease which was a direct protest against certain of the current material concepts. He taught that the life of all lower animals was subject to mechanical, materialistic laws, but that man constituted the unique exception among living beings. In man, the thing of supreme importance is the "soul" or "anima." The special end of the human

body, he believed, is to house the soul; all chemical and physical processes of the body are governed by this sensitive "anima," which pervades all bodily parts and presides over all events. When the body is diseased, the symptoms are the efforts of the soul to free itself from morbid influences, and to restore normal movements in the organism.

Friedrich Hoffmann (1660–1742) was the first professor of medicine in the University of Halle, being appointed in 1693, and Stahl was one of his colleagues. Apparently he endeavored to reconcile the "spiritual" and "material" theories of health and disease. He taught that life depends upon a universally diffused ether in the atmosphere. Animals, including man, breathe in the ether, which pervades the entire body; accumulating in the brain it generates the "nervous fluid" or pneuma. Health is dependent upon the maintenance of a proper body "tonus," a composte of regular action and reaction, contraction and relaxation; disease results from a disturbance of this tonus. Hoffmann divided diseases into (1) atonic diseases, due to relaxations in the capillaries of the vascular system, and (2) congestive and inflammatory diseases, caused by contractions of the capillaries.

Sauvages and Cullen. François Boissier de Sauvages (1706–1767) attempted to carry out Sydenham's idea of describing

diseases as botanists describe plants. In his "Traité des Classes des Maladies" (1731) and in his larger treatise "Nosologia methodica sistens morborum Classes, Genera et Species" (1763), he enumerated 2400 different kinds of diseases, which he subdivided into 10 classes, these latter into 40 orders, the orders into genera, and the genera into species. What he actually did was to classify every symptom as a disease. Cullen, and others, attempted somewhat similar classifications during the eighteenth century.[63]

William Cullen (1710–1790), professor of medicine at Edinburgh, attempted in his "Nosology or Classification of Diseases" a classification of diseases upon a natural history plan, most of which is now forgotten. Largely influenced by the new physiological doctrine of irritability expounded by Albrecht von Haller (1708–1777), Cullen attempted to build a system of medicine upon this doctrine. In his "First Lines of the Practice of Physic" he also stresses the importance of nervous action, and he lists "gout" as a neurosis.

Brown and Hahnemann. John Brown (1735–1788) was another medical systematist of the eighteenth century whose contemporary fame far outweighed his actual contributions to the advancement of man's ideas of disease. Brown's theory of medicine, sometimes called the Brunonian system, was based upon the property of

"excitability." In his own words: "The whole phenomena of life, health as well as disease, consist in stimulus and nothing else." According to his theory, all diseases fall into one of two categories (1) asthenic, to which 97 per cent of all diseases belong and which require stimulating treatment, and (2) sthenic, which require sedative treatment. Brown's wordy, dialectic system, founded on abstract theory, had a great vogue in Italy and Austria, but it retarded rather than advanced medical knowledge.

Samuel Hahnemann (1753–1844), the father of homeopathy, was the last of the group of eighteenth century theorizers. Paracelsian in his attitude, he taught that all that matters is a knowledge of symptoms; the attempt to go behind symptoms and discover their causes he considered a bootless task. Morbid anatomy and pathology he discarded. Hahnemann not alone revived Paracelsus' doctrine of signatures, but he introduced into therapy the doctrine that the more a drug is diluted the more powerful its action becomes. Hahnemann's insistence upon the use of infinitesimally small doses of drugs in the treatment of disease, although based upon improper reasoning, was of undoubted value in an age when physician tended to over-drug their patients. With such a dogmatic and non-scientific method of approach, it is no matter of surprise to find that Hahne-

mann held most bizarre ideas of disease. His ideas in regard to chronic maladies are particularly quaint; all of them, excepting those caused by medicines, arise from three diseases: (1) psora, or the itch, a skin disease which, when driven inwards, is responsible for seven-eighths of all chronic maladies: (2) syphilis, and (3) sycosis (another skin disease).

It is not fair to end this brief account of eighteenth century theoretical systematists without stressing the fact that the century witnessed the acquisition of a considerable body of actual, practical knowledge of disease. The clinical investigations of John Fothergill on diphtheria and tic douloureux and of John Huxham and John Pringle on epidemic fevers in England are especially notable. And from the Viennese school, during the eighteenth century, appeared an invention whose inestimable value in clinical studies was not recognized until the early part of the following century. This was Leopold Auenbrugger's report of his discovery of a method of diagnosing diseases, particularly of the chest, by direct percussion, published in his "Inventum novum" in 1761. The contributions of Morgagni, Bichat and Jenner will be detailed separately.

The Rise of Modern Pathology. With Morgagni modern pathology begins; in fact it is accurate to state that upon the method of Sydenham and the method of

Morgagni much of modern medicine rests. Sydenham's great contribution to the advancement of knowledge of disease lay in his rigid insistence upon the necessity of exact observations on the natural history of disease; Morgagni's inestimable service lay in his insistence upon thoroughness and accuracy of detail in the study of morbid anatomy. Sydenham emphasized the importance of accurately reading the story of disease from the book of the living sick body; Morgagni stressed the importance of reading with scrupulously careful, naked eyes the grewsome story from the telltale marks and lesions that disease leaves upon the bodies of those that it has slain, and attempting to correlate them with the symptoms which the patient presented during his illness.

Giovanni Battista Morgagni (1682–1771) was born in Forli, Italy, and graduated in medicine at Bologna. In 1712 he was called to Padua, where he soon became professor of anatomy. The masterpiece by which he is most widely known is his great book "De Sedibus et Causis Morborum per Anatomen Indagatis" Venice, (1761), which did not appear until he was almost eighty years of age. It was published as a series of letters to a young friend interested in science, in which he detailed the fruit of sixty years' intensive study of the appearances encountered by him at postmortem examinations, as well

as of the symptoms during life, in a number of cases of various diseases which he had studied. Actually, it was a clinical work in which detailed anatomic explanations of disease symptoms were given. In all, the work covers about seven hundred autopsies, most of which Morgagni performed himself. His descriptions of the gross pathology of lesions of the blood vessels, particularly of aneurysms, and his clarification of the confused subject of the symptomatology and gross pathology of pneumonia were particularly masterly, although there was scarcely any phase of "naked eye" pathology, including tumors, which he left untouched.

Morgagni, replying upon naked-eye examinations, thought in terms of whole organs of the body being diseased; he not only made valuable contributions to gross pathology but he brought it far along the road that it has since followed. It remained for Bichat to demonstrate that the various organs of the body are separable into "textures" or tissues, and to show how the separate involvement of different tissues by different diseases gives rise to different morbid symptoms.

Marie-François-Xavier Bichat (1771–1802) spanned in his short and tragic life the revolutionary sunset of the eighteenth century and the first faint dawn of the nineteenth century. Born in Thoirette, France, he studied medicine in Lyons,

and in 1794 came to Paris. A sufferer from tuberculosis during all the productive years of his life, he spent the whole of his days in the dissecting room, and wrote at night, dying at the age of thirty-one years. Yet in the short space of eight years which he spent in Paris, Bichat not alone revolutionized anatomy and physiology, but he introduced a new concept into man's ideas of the nature of disease. His "Treatise on Membranes" (1799–1800) is looked upon as constituting the foundation upon which the science of histology has been reared, but his huge "Anatomie générale" (1801–1802) is probably his most classic contribution. In this latter volume he says:

> All animals are an assemblage of different organs, which, executing each a specific function, concur for the preservation of the whole. These in turn are made up of many textures (tissues) of different kinds, which really compose the elements of these organs. Just as chemistry has its simple bodies, uniting to form compounds; so anatomy has its simple tissues which by their combinations make up organs.

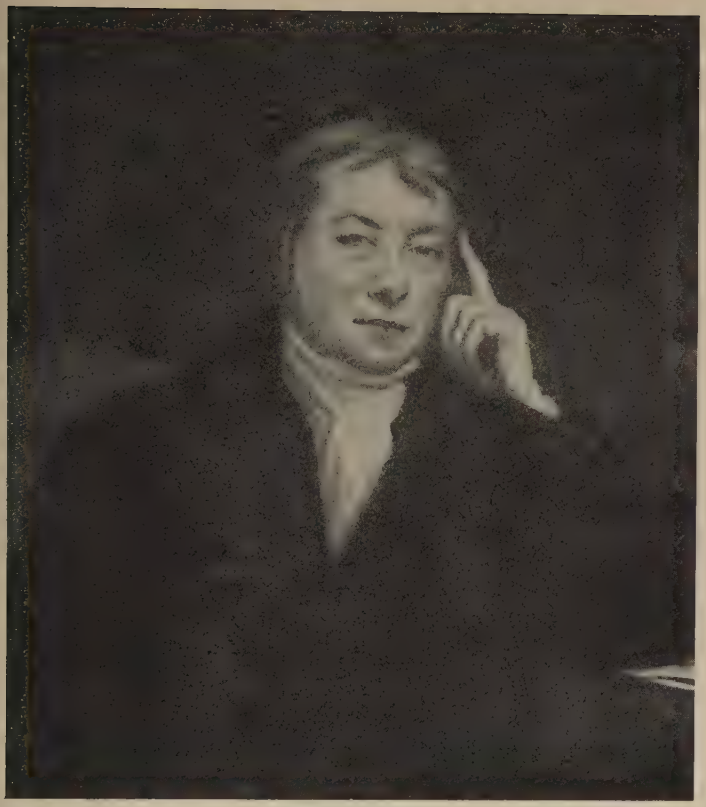
Next he distinguishes twenty-one different tissues, including nervous, connective, vascular, muscular, osseous. glandular, etc. In this differentiation of various organs of the body into their component tissues, Bichat did not employ the microscope; he dissected with fine instruments and, as he writes: "submitted tissues to

the action of various chemical reagents as heat, air, water, acids, alkalies, salts, desiccation, maceration, putrefaction, boiling, etc., fixing with precision the limits of each organized tissue."[64]

It is to Bichat's everlasting credit that he did not rest content with his morphological discoveries. Prior to him, students of pathology, such as Morgagni, thought almost exclusively in terms of whole organs being diseased. Bichat dissociated morbid changes in an organ into diseases of the various tissues of which the organ is composed, and showed how, frequently, each followed a different course.

THE SCIENTIFIC BEGINNING OF IMMUNOLOGY

Jenner. Inoculation against smallpox is said to have been practiced in China since remotest times, as well as in India and Persia, but no reliable data are available as to the exact antiquity and extent of the practice.[65] It was not until 1717 that Lady Montagu, wife of the British ambassador to Turkey, introduced variolation into Europe from Constantinople. Although the practice of "variolation," the dangerous practice of passing mild smallpox from one person to another by inoculation of material from smallpox pustules, had been practiced for centuries, it is to Edward Jenner (1749–1823) that the world owes the safer method of small-



Edward Jenner.
(1749–1823)

pox vaccination which it practices today. Jenner's pioneer experimental work on the prevention of smallpox not only marked the beginnings of a new era in medicine, but it constituted the scientific foundation upon which the science of immunology has been erected.

Born at Berkeley, Gloucestershire, England, on May 17, 1749, Jenner went to London in 1770 and became a resident pupil, and a lifelong friend, of the famous surgeon and anatomist, John Hunter. In 1773, he took up the practice of medicine at Berkeley, where he died on January 26, 1823.

The current belief in rural England, as epitomized by the statement of a Gloucestershire diary maid: "I cannot take the smallpox because I have had the cowpox," formed the background of Jenner's discovery. His first, and crucial, experiment in smallpox vaccination (the word vaccination is derived from "*vacca*," a cow) was made on May 14, 1796, when he inoculated James Phipps, a boy of eight years, with cowpox. After the boy's recovery, he inoculated him with virulent smallpox virus, and the boy failed to contract smallpox.

Here are Jenner's own words:

> The first experiment was made upon a lad of the name of Phipps, in whose arm a little vaccine virus was inserted, taken from the hand of a young woman who had been accidentally infected by a cow. Notwithstanding the resem-

blance which the pustule, thus excited on the boy's arm, bore to variolous inoculation, yet as the indisposition attending it was barely perceptible, I could scarcely persuade myself the patient was secure from the Small Pox. However, on his being inoculated some months afterwards, it proved that he was secure.

Jenner's first paper on his discovery was never printed; it was not until 1798 that his first treatise entitled "An Inquiry into the Causes and Effects of the Variolae Vaccinae, or Cow Pox" appeared. In 1799 was published his second treatise "Further Observations on the Variolae Vaccinae, or Cow Pox" and in 1800 the third, "A Continuation of Facts and Observations Relative to the Variolae Vaccinae, or Cow Pox."[67]

Although the immediate reception given by the medical profession to his discovery was not highly encouraging, yet in 1802 Parliament voted Jenner £10,000 and, in 1806, £20,000 in recognition of the scientific value of his services to humanity, and as early as 1807 Bavaria made vaccination against smallpox compulsory.

Jenner's three treatises constitute the first scientific proof ever advanced that a highly contagious disease such as smallpox is preventable by conveying a closely allied disease, cowpox, to man; as such they can be considered to mark the real beginnings of the science of immunology, whose further development awaited the genius

of Pasteur eighty years later. Thomas Jefferson wrote to Jenner the following:

> Medicine has never before produced any single improvement of such utility. Harvey's discovery of the circulation of the blood was a beautiful addition to our knowledge of the ancient economy, but on a review of the practice of medicine before and since that epoch, I do not see any great amelioration which has been derived from that discovery. You have erased from the calendar of human afflictions one of its greatest. Yours is the comfortable reflection that Mankind can never forget that you have lived; future generations will know by history only that the loathsome smallpox has existed, and by you has been extirpated.

It is not equally well known that Jenner,[68] in 1798, was probably the first specifically to call attention to allergy as it occurs in an infectious disease. In reporting upon the case of a woman who had cowpox thirty-one years previously, he called attention to the sudden development of an "efflorescence of a palish red color" around the skin areas where variolous matter had been injected. Continuing, Jenner wrote: "It is remarkable that variolous matter, when the system is disposed to reject it, should excite inflammation on the part to which it is applied more speedily than when it produces the smallpox. Indeed, it becomes almost a criterion by which we can determine whether the infection will be received

or not. It seems as if a change, which endures through life, had been produced in the action, or disposition to action, in the vessels of the skin; and it is remarkable, too, that whether this change has been effected by the smallpox or the cowpox, that the disposition to sudden cuticular inflammation is the same on the application of variolous matter."

Chapter IV

THE NINETEENTH CENTURY

THE first half of the nineteenth century witnessed the definite beginnings of a truly scientific orientation of man's ideas of disease. To a considerable extent this was made possible by refinements in method, by means of which improved microscopes and other instruments of precision were brought to bear upon the age-old mystery of health and disease. Because there was almost a relentless chronological progression in man's attack upon these problems throughout the century, and because, for the first time, public acceptance of hard-won scientific facts did not lag so far behind the discoveries, but often joyfully kept pace with them, it has seemed advisable to write the story of the past century as a more or less continuous narrative, picturing the development of pathology and chemistry, the final overthrow of the doctrine of spontaneous generation, and the rise of the new science of bacteriology and immunology as the unfolding of scientific developments which made the orientation and clarification of man's ideas regarding the nature of disease almost a scientific inevitability. Great human figures arose; old misconceptions tottered and collapsed; and through it all the relentless fingers

of the new century were weaving into the warp of the cloth of truth threads of fact supplied by the bound and tramelled hands of scientific workers of the past and by the freer hands of contemporary scientists. And yet, in a century of unprecedented discovery, there were three great scientific figures who, more than any others, influenced and molded the direction of thought upon the nature of disease processes. These three men were the pathologist Virchow, a German, the naturalist Darwin, an Englishman, and the chemist and biologist Pasteur, a Frenchman. This triad affords a most instructive example of how not only diverse nationalities, but different fields of science, collaborated to place man's knowledge of disease upon a surer foundation.

Converging observations and discoveries were at work during the early part of the nineteenth century, preparing the soil in which it was possible for a Virchow to germinate. It was a period of fact-assembling; unbridled theorizing upon the nature of disease such as characterized the eighteenth century was largely in abeyance; science awaited the accumulation of more exact facts. Contributing to this latter development was the publication, in 1806, of Corvisart's "Essai sur les Maladies et les Lesions Organiques du Coeur et des Gros Vaisseaux," in which he stressed the importance of the study

of the pathological changes in the organs as a means of acquiring definite knowledge of the nature of disease processes.

Laënnec. The real genius in this direction, however, was Réné Théophile Hyacinthe Laënnec (1781–1826) whose "Traite de l'Auscultation Médiate," published in 1819, marks an epoch. It was in 1816 that he conceived the idea of indirect auscultation, out of which the invention of the stethescope developed in 1817, an instrument which wrought a revolutionary change in the physician's method of approach to problems of diagnosis. Before Laënnec's time, a physician's examination of a patient was largely as follows; he observed his appearance, felt his pulse, looked at his tongue, examined his urine. Now, for the first time, a really objective examination of organs, particularly those of the chest, was made possible. By comparing his stethescopic findings on the living patient with the post-mortem findings, Laënnec elucidated men's conceptions of various diseases; particularly was this true of tuberculosis. Prior to Laënnec, the early stages of tuberculosis were little known, and, in its advanced stages, it was often hopelessly confused with such chronic pulmonary conditions as bronchitis, empyema, gangrene, etc. Moreover, such medical systematists as Sauvages had listed as many as twenty varieties of pulmonary tuberculosis, basing their conclusions on

Réné Théophile Hyacinthe Laënnec.
(1781–1826)

symptom observation. Laënnec not only showed that all of these so-called varieties were merely stages in one disease, tuberculosis, but he demonstrated that tuberculosis of the lungs is a special disease, differing from other disease processes, and that tuberculosis of other organs, as well as scrofula, were merely manifestations of the same general disease. Laënnec, who died at the age of only forty-five years, was also the first to describe emphysema, bronchiectasis and gangrene of the lungs, as well as to differentiate pneumonia from bronchitis and pleuritis.

Following Laënnec came other outstanding members of the French School, such as Louis, Andral, Bretonneau and others, whose researches led not only to further advances in the knowledge of various diseases, but to continual discoveries of new diseases, as well. As examples may be mentioned Pierre Bretonneau's (1771–1862) description of diphtheria. It was he who gave the disease its present name and was the first clinically to differentiate it from scarlet fever; in the same treatise he gave his classic demonstration of the specific character of different diseases, contained in his book which appeared in 1826.[69] Pierre C. A. Louis, in 1829, published his pioneer on typhoid fever[70] in which he gave its present name to the disease. And Gabriel Andral, in his Clinique

médicale (1829–33), made an outstanding contribution to clinical medicine.

From Paris, the clinical-scientific revolution initiated by the French School led to the development of similar clinical schools in England and Ireland and Germany and America. In Dublin, from 1820 on, arose such physicians as Graves, Cheyne, Stokes, Adams and Corrigan; in London such pioneers as Addison and Bright, in Germany, Skoda and Rokitansky, and in America such medical figures as Gerhard. With all of them, emphasis was placed on the importance of a combination of anatomical-pathological-clinical investigation in elucidating the nature of disease processes. As Graves expressed it in one of his clinical lectures:[71]

> In order justly to estimate the importance of morbid anatomy, we should recollect that the first alteration in the picture of a part is not the cause but the consequence of disease . . . Thus the physical alterations which attend external inflammation, the tumefaction, the heat, the redness are not the cause but the consequences of disease. But in thus reducing them to the rank of symptoms, do we diminish their importance? Certainly not. For being immediately connected, as effects, with the *primary* cause, they prove the most useful of all symptoms, in enabling us to ascertain the seat and progress of diseased action.

Now, stimulated by the French physiologist Magendie, there arose what has

Josef Skoda.
(1805–1881)

Carl Rokitansky.
(1804–1878)

been called the School of German Physiological Medicine, which postulated that pathological phenomena are merely modified physiological phenomena, and that, therefore, the complete elucidation of the nature of disease processes is to be obtained not merely by a study of the changes in the various organs after death, but by experimental physiology as well. Members of this School include such distinguished names as those of Schwann, Remak, Wunderlich, Henle, Traube, Frerichs, Virchow, Helmholtz, du Bois-Reymond, etc. Wunderlich, in his "Geschichte der Medizin" (1869), clearly defines the reason for his insistence on the name "physiological medicine":

> On the one hand, it was chosen to express the fact that pathology, in contrast to all ontological and personifying conceptions, is only the physiology of diseased man; on the other hand, to call to mind the fact that pathology requires the same means and methods to establish facts, and the same logic in argumentation, as were already recognized in the science of healthy man.

And Virchow, in his famous treatise "Die Einheitsbestrebungen in der wissenschaftlichen Medizin" (1849) wrote: "The subjects of therapy are not diseases but conditions; we are everywhere concerned only with changes in the conditions of life. Disease is nothing but life under

altered conditions." The great advance of the German Physiological School of Medicine lay in the fact that it stressed the absolute importance of learning the relations between pathological phenomena, whereas the French school had confined itself largely to a minute description of the clinical and pathologico-anatomical phenomena of disease processes.

Just as Bichat, earlier in the nineteenth century, marked an epochal advance by his general anatomy, so Virchow, through his cellular pathology and his proof that all cells come from parent cells, as well as by his cellular studies on such diseases as tuberculosis and tumors, became a pioneer in turning the direction of medical and scientific researches towards the cell, as constituting the ultimate basis from which knowledge of both health and disease is to be derived.

Rudolph Virchow (1821–1902), who is quite generally regarded as the greatest pathologist the world has ever known, was born in Schievelbein, Pomerania. He graduated in Berlin in 1843, and in 1847 he and Reinhardt founded the *Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*, which even today is the leading journal of pathological anatomy in the world, and is everywhere known as *Virchow's Archiv*. In 1846 appeared Virchow's classic researches on thrombosis and embolism;[72] then followed his no

Rudolph Virchow.
(1821–1902)

less[73] classic work on pyemia and septicaemia, his discovery of leukemia, his pioneer investigations on degenerations, and his researches on the specific cellular constituents of tumors.[74] But the great, outstanding contribution of Virchow was that he rebuilt the science of pathology, making it a cellular pathology, in place of the previous science in which cells had no part. It is to him that the scientific world owes its conception of the human body as being an organized, and continually developing, cell state, in which each microscopic unit, or cell, plays its part; a conception which has done much to clarify men's ideas of not alone inflammations, degenerations, etc., but of tumors as well. It was Virchow who taught pathologists to look to the cell as constituting the microscopic field in which the ravages and the telltale marks of disease are best to be read, a lesson made possible largely by marked improvements in microscopes which were made during the first half of the nineteenth century.

Coincident with these advances, new methods, microscopical, mechanical and chemical, were introduced into clinical medicine, and thereby contributed to a further elucidation of the nature of certain disease processes. As early as 1843, Andral published his "Essai d'hematologie, pathologique," Paris, in which, among other innovations, he described methods for

determining the amount of fibrin and of corpuscles in the blood, and of albumin in serum, by weight; studies which laid the foundations of hematology. Again, in 1852, Vierordt, a physiologist, introduced methods for counting blood cells, and in 1855, he employed the sphygmograph for studying the pulse. Helmholtz, another physiologist, invented the ophthalmoscope in 1850; and Trommer and Heller, physiological chemists, introduced chemical methods for the study of the urine. And in France, during this period, the great physiologist Claude Bernard was continuing his researches in experimental physiology, out of which resulted such monumental contributions to science as his studies on the nature of glycosuria, on pancreatic digestion, and on the circulatory and heat-regulating mechanisms of the body. Indicative of his attitude toward science, Claude Bernard once said:

> Put off your imagination, as you take off your overcoat when you enter the laboratory; but put it on again as you do your overcoat, when you leave the laboratory. Before the experiment, and between whiles, let your imagination wrap you around; put it right away from you during the experiment itself, lest it hinder your observing power.

While these developments in pathology and chemistry were transpiring, certain important technical advances were made

possible by improved microscopes, and there occurred a greater centering of attention upon the hitherto little known bacteria. Coincident with these discoveries relating to microscopic life, the inevitable battle over the doctrine of spontaneous generation flared up anew. We find that the year 1835 assumes importance because that year was signalized by improvements in the achromatic lens and very shortly important fruits of this technical advance appeared. In 1837, Latour, Schwann[75] and Kutzing independently studied the microscopic yeast cells in fermenting beer and wine, cells previously seen by van Leeuwenhoek and named *Mycoderma cerevisiae* by Desmazieres. It is to Schwann that credit is due for discovering the living, organic nature of the yeast cell. In the same year Agostino Bassi (1773–1856), an Italian, investigated a contagious disease of the silkworm known as muscardin, and showed that the disease was transmitted by the passage from infected to healthy worms of minute, glittering particles (spores) of a minute plant, a yeast subsequently renamed *Torula cerevisiae* by Turpin. Bassi prophesied that just as he had shown the relation of a certain type of microorganisms to a disease of silkworms, so would animal or vegetable microbes be discovered some day to be the cause of such human diseases as smallpox, plague and syphilis.

During this time, Franz Schulze, in 1836, and in 1837 Theodor Schwann, the founder of the cell theory, turned their attention to the doctrine of spontaneous generation. They repeated the experiments of Needham and Spallanzani, directing particular attention to the troublesome oxygen factor introduced by Priestley's discovery.

Schulze employed a flask containing nutrient fluids, plugged with a large perforated cork through which connections were made by means of bent glass tubes with a series of bulbs containing sulphuric acid and other acid solutions. By means of an aspirator, air was sucked through the acid, in order to remove the floating germs in the air, before the air reached the culture flasks. Schulze found that when such chemically purified air was drawn into flasks containing previously boiled nutrient fluids, the culture media remained sterile, although the air drawn into the flasks contained unaltered oxygen. Tyndell,[76] commenting on these experiments, says:

> Here again the success of Schulze was due to his working in comparatively pure air, but even in such air his experiment is a risky one. Germs will pass unwetted and unscathed through sulphuric acid unless the most special care is taken to detain them. I have repeatedly failed, by repeating Schulze's experiments, to obtain his results. Others have failed like-

wise. The air passes in bubbles through the bulbs, and to render the method secure, the passage of the air must be so slow as to cause the whole of its floating matter, even to the very core of each bubble, to touch the surrounding fluid. But if this precaution be observed water will be found quite as effectual as sulphuric acid.

Schwann[77] (1837) used an apparatus somewhat similar to Schulze's, except that he drew the air for his culture flasks through a bent tube surrounded by a jacket of highly heated metal, thereby obtaining a germ-free air through high heating, rather than by washing the air in acid. He, likewise, reported that his flasks of media remained sterile.

Objections were still raised against the experiments of both Schulze and Schwann, mainly on the basis that the oxygen admitted to the culture flasks might be changed in its properties through passage through acid, and by extreme heat, thereby rendering it unable to support life. Schroeder and Dusch, in 1854, met this objection by showing that sterilized culture media in flasks plugged merely with cotton, which allowed of ingress of chemically and physically unaltered air, remained sterile if proper precautions in sterilization were observed.

In 1838 Ehrenberg,[78] employing improved microscopes, introduced a classification of microscopic microorganisms which is

employed, with minor modifications, at the present time. He introduced the term *Vibriones* to include the microscopical forms, which he subdivided into four species: (1) the rigid filamentous bacterium, (2) the flexuous filamentous vibrio, (3) the rigid filamentous spirillum and (4) the flexuous filamentous spirocheta. In 1839, the parasites of favus and thrush were observed.

In 1840, Jacob Henle, the distinguished anatomist, after a careful weighing of the evidence, concluded that there is a causal relationship between the minute, living microorganisms or fungi and disease.[79] Because of the fact that he not only collected and adjudged the work of previous investigators, but also rigorously investigated the subject himself, Henle has been termed the real propounder of the Germ Theory of Disease. With the relatively crude methods at his disposal, he was unable to satisfy the requirements he formulated as being essential to the proof of the theory, requirements, incidentally, which he so ably formulated that they are almost identical with the postulates laid down by Koch, years later, as being necessary of fulfillment before a definite relationship can be established between a given microorganism and a given disease.

As Ford[80] says: "The year 1840 may be said to mark the beginning of the modern science of bacteriology."

In 1840, Felix Dujardin, using microscopes with a magnification of from 300 to 1200 diameters, described microorganisms in such conditions as favus, herpes tonsurans, pityriasis versicolor and soor, as well as in typhoid ulcers and in the nasal secretions of glandered horses. His observations, as well as those of his contemporaries, were made on unstained fluid preparations, or on preparations stained by carmine and indigo. In 1842, Goodsir, the Scotch surgeon, discovered *Sarcina ventriculi* in stomach contents, and in 1843. Oliver Wendell Holmes, the distinguished New England physician, poet and essayist, published his classic "On the Contagiousness of Puerperal Fever."[81] Four years later, in 1847, Semmelweiss, of Vienna, announced his belief that puerperal fever depended upon poisons carried by the fingers of physicians and students to the woman in childbed.[82]

In 1849 Pollender,[83] and in 1850 Davaine, described the anthrax bacillus in the blood of animals dying, and dead, of anthrax, but were very conservative in the matter of attributing etiological significance to the microorganism; and in 1853 Delafond produced anthrax in animals and showed that only when anthrax bacilli are present in the b ood is such blood experimentally infective for healthy animals.

In 1854, Schroeder and von Dusch introduced the use of cotton as air filters

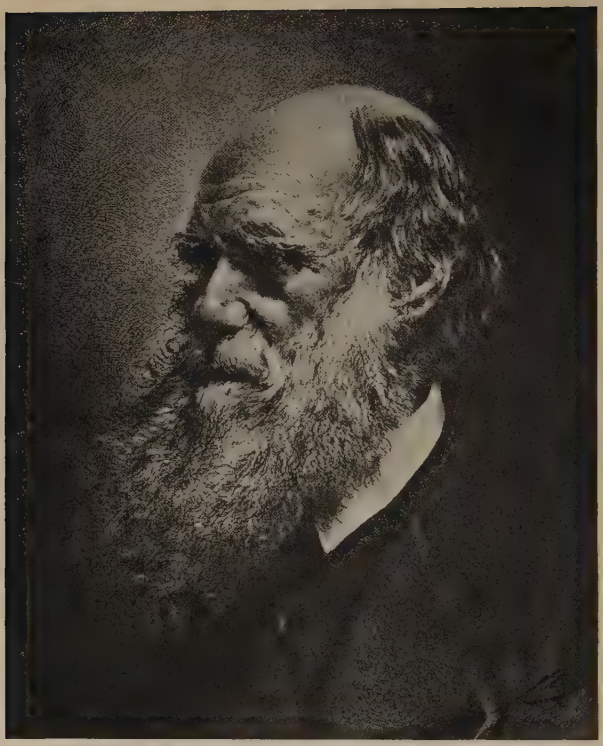
Oliver Wendell Holmes.
(1809–1894)

in flasks and test tubes, showing that dry cotton plugs prevent the entrance of air microorganisms into previously sterilized receptacles.

The world of science was on the threshold of monumental discoveries; and now enters upon the stage Darwin, the immortal activator.

Darwin. There have been few books in the history of the world that have caused a more profound revolution in men's thoughts than Darwin's "Origin of Species," published on November 24, 1859. Charles Robert Darwin (1809–1882) was born at Shrewsbury, England, where his early education was obtained; later he matriculated at Cambridge, where he graduated in 1831. An intensely human sidelight upon the ill-health with which Darwin was inflicted is afforded by the following words written by his son Francis:[84]

> No one indeed, except my mother, knows the full amount of suffering he endured, or the full amount of his wonderful patience. For all the latter years of his life she never left him for a night; and her days were so planned that all his resting hours might be shared with her. She shielded him from every avoidable annoyance, and omitted nothing that might save him trouble, or prevent him becoming over-tired, or that might alleviate the many discomforts of his ill-health. I hesitate to speak thus freely of a thing so sacred as the life-



Charles Robert Darwin.
(1809–1882)

long devotion which prompted all this constant and tender care. But it is, I repeat, a principal feature of his life that for nearly forty years he never knew one day of the health of ordinary men, and that thus his life was one long struggle against the weariness and strain of sickness. And this cannot be told without speaking of the one condition which enabled him to bear the strain and fight out the struggle to the end.

The full title of Darwin's masterpiece was "On The Origin of Species by means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life." The almost immediate effect of this book upon scientific minds was one of liberation; the previously hidebound, conventional view that natural events, including disease, moved in immutable channels lost its attractiveness; daring vistas began to open in the thoughts of men. For static immutability was substituted the rejuvenating concept of perpetual flux. Time-honored classifications of diseases, based upon superficial resemblances, began to be doubted; suddenly the minds of medical men were stirred with the thought that not only are diseases phases of the flow of natural processes operative throughout the living universe, but hope began to be born that it might be possible for science to pierce to the actual origins of disease, instead of merely cataloging its manifestations and ravages in the body. More-

over, the "Origin of Species," with its first five chapters which explained artificial selection and the operation of natural selection because of the struggle for existence, as well as the laws of variations and the causes of modifications, centered scientific minds upon heredity and the possible heredity of certain diseases.

Fortunately for the cause of medical science, Darwin's "Origin of Species," and the multiplicity of speculations to which it immediately gave birth, appeared at the time when not only were experimental methods being rapidly perfected, but even more important the great, liberating figure of Pasteur was looming upon the scientific horizon.

The proper introduction to Pasteur is best made by picking up the threads of the controversy over spontaneous generation which, as we have seen, received a temporary new lease of life in the early part of the nineteenth century. This largely resulted from the fact that widely divergent ideas in regard to the nature of fermentation were held at this time. Berzelius, the Swedish chemist, believed that fermentation resulted from a catalytic force, i.e. by contact. He dismissed the yeast cells, described by Latour in fermenting beer and wine, by saying that what Latour had seen was but "an immediate vegetable principle, which became precipitated during the fermentation of beer

and which, in precipitating, presented forms analogous to the simpler forms of vegetable life, but formation does not constitute life." Liebig, the German chemist, believed that the ferment itself came from dead protein materials. In contrast to Berzelius' theory of "contact," Liebig taught a theory of "influence"; and these two theories of fermentation reigned almost supreme in the early 50's of the nineteenth century.

Now into the lists steps a Frenchman, Pouchet, director of the Natural History Museum of Rouen, whose main bid to fame lies in the fact that he was the activator of Pasteur's monumental experiments on the nature of fermentation. On December 20, 1858, Pouchet sent to the Acadèmie des Sciences a "Note on Vegetable and Animal Proto-organisms Spontaneously Generated in Artificial Air and Oxygen Gas." An index to his false mental approach is vouchsafed by the following opening sentence from his book on Heterogenesis: "*When, by meditation,* it was evident to me that spontaneous generation was one of the means employed by nature for the production of living beings, I applied myself to discover by what means one could place these phenomena in evidence." In his note to the Academie Pouchet, after insisting on the excessive precautions he had taken to exclude all sources of error in his experiments, declared

that he was prepared to demonstrate that "animals and plants could be generated in a medium absolutely free from atmospheric air, and in which, therefore, no germ of organic bodies could have been brought by air." The crucial experiment performed by Pouchet was as follows: After filling a flask with boiling water and carefully sealing it, he inverted it and thrust the neck into a bath of mercury. When the water had cooled, he opened the neck of the flask, still under the mercury, and connected it with an oxygen-liberating retort. By heating the retort, he bubbled oxygen into the flask, thus replacing some of the water. When about half of the water was displaced by oxygen, Pouchet took a small amount of hay, previously heated in an oven to a high temperature, and pushed the hay, grasped in a pair of sterile forceps, underneath the mercury and into the mouth of the flask. Thus he produced a hay infusion in contact with pure oxygen. After a few days' incubation, the infusion became cloudy and, under the microscope, it was found to be teeming with micro-organisms.

In introducing the experiment described, Pouchet wrote:

> The opponents of spontaneous generation assert that the germs of microscopic organisms exist in the air, which transports them to a distance. What, then, will these opponents say if I succeed in introducing the generation

of living organisms, while substituting artificial air for that of the atmosphere?"

And, at what he considered the triumphant conclusion of his experiment, he wrote:

> Where does this life come from? It cannot come from the water which had been boiled, destroying all living germs that may have existed in temperature of incandescence. It cannot have been carried in the hay, which had been heated for a long period before being introduced into the water.

Therefore, Pouchet declared this life in his flask to be of spontaneous origin.

Pasteur. Now is the stage set for the entrance of Louis Pasteur. Born on December 27, 1822, in an humble house in Dole, France, his father a tanner and a sergeant in the 3rd Regiment of Napoleon, his mother the daughter of an humble gardener of Marnoz, the boy gave no particular indication of the brilliant career that was to be his as a man. When, at the age of twenty, he went up for his examination for the *Baccalaureat des sciences* before the Dijon Faculty he was put down as "mediocre" in chemistry. And when, a few weeks later, he took his examinations for the École Normale, he passed only fifteenth out of twenty-two candidates. However, the following year he was admitted fourth on the list.

His first scientific recognition came to Pasteur in the fields of chemistry and

Louis Pasteur.
(1822–1895)

molecular physics, in which he had pursued researches from the time he left normal school. He showed that crystals of certain tartrates, chemically and physically similar except in the fact that they each had their special hemihedral facets, acted differently when their solutions were examined under a polariscope. In his own words:[85]

> I separated with care the right and left handed hemihedral crystals and observed separately their solutions in the polarization apparatus. Then, with no less surprise than joy, I saw that the right-handed hemihedral crystals turned to the right and the left-handed ones to the left the plane of polarization, and when I took equal weights of each of these kinds of crystals the mixed solution was neutral to polarized light because of the neutralization of the two equal and opposite individual deviations.

From these, he proceeded to study the aspartates and malates and, as Duclaux says:[86] "Thus, little by little, was born in his hands the science of the arrangement of atoms (stereochemistry), which has since attained so much importance. Wherever he went Pasteur was an initiator."

One day, in 1853, Pasteur said:[87]

> The Universe is a dissymmetrical whole. I am inclined to think that life, as manifested to us, must be a function of the dissymmetry of the universe and of the consequences it produces. The universe is dissymmetrical,

for if the whole of the bodies which compose the solar system were placed before a glass moving with their individual movements, the image in the glass could not be superposed to the reality.

And again: "Life is dominated by dissymmetrical actions; I can even foresee that all living species are primordially, in their structure, in their external forms, functions of cosmic dissymmetry." All of his life Pasteur retained a regret that he was not able to complete his studies on crystallography. At the age of seventy, he said:

If I have a regret, it is that I did not follow that route, less rude it seems to me, which would have led, I am convinced, to wonderful discoveries. A sudden turn threw me into the study of fermentation, fermentations set me at diseases, but I am still inconsolable to think that I have never had the time to go back to my old subject.

In 1857, Pasteur went to Paris as director of scientific studies in the École Normale, and there, in an almost uninhabitable garret, he pursued his studies on fermentation which culminated in the following brilliant demonstration: (Duclaux[88])

Fermentation is no longer a vague transformation, indeterminate in its cause and in its origins, capable of taking place under the influence of any organic substance whatsoever; it is a specific phenomenon, due also

to the existence and development of a specific organism, the study of which under the microscope is facilitated in proportion as we remove from the liquid undergoing fermentation those insoluble organic substances which it was formerly believed necessary to add to it. Since, by working with a clear bouillon, it is possible to follow closely the organism sown, and to be sure that the bouillon contains this and this alone, the study of its nutrition becomes easy. Now, by acting on the nutrition of an organism, we become the master of it; we can sow it and cultivate it with as much certainty, and with the same absence of weeds, as we can cultivate lettuce in a garden. We can also banish it from liquids where there is no occasion for its presence. In short, this infinitely small organism becomes tangible, and open to experiment; a capital idea which the whole life of Pasteur will henceforth be spent in developing.

In his article on lactic fermentation, Pasteur[89] showed that fermentation is a vital act, brought about by a yeast; he advanced the idea of a specific, living ferment for each fermentation, and ended with these words:

It is now my opinion as the result of the knowledge that I have gained on this subject, that whoever will judge impartially the results of this work and those which I shall study in the near future, will recognize with me that fermentation is correlative with life, with the organization of globules, not with the death or putrefaction of these globules; neither does it appear to be a phenomenon of contact where

the transformation of the sugar takes place in the presence of the ferment without giving anything to it or taking anything from it. These latter affirmations, one will soon see, are contradicted by experiment.

In 1860, Pasteur[90] proved that both lactic fermentation (the souring of milk) and alcoholic fermentation are due to the growth of microscopic organisms. His crucial experiment consisted in growing the yeast in a liquid deprived of all nitrogenous organic matter, one containing only pure cane-sugar, various mineral salts, and an ammonia salt to supply the cells with nitrogen. In this medium the yeast cells developed, and multiplied, and caused fermentation. Thus not only was Liebig's theory of fermentation demolished, which claimed that organic nitrogenous matter was necessary for fermentation to occur, but that of Berzelius as well, which postulated that the ferment exerted its action only by its presence (catalysis), remaining unchanged in quantity and quality throughout the process.

Pasteur had now demonstrated that ferments are living beings, and that for each kind of fermentation there is a special corresponding ferment. At this time (1860) we find him writing in a letter to his father: "God grant that by my persevering labours I may bring a little stone to the frail and ill-assured edifice of our knowledge of those deep mysteries of Life and Death

where all our intellects have so lamentably failed."

From now on we find Pasteur embarked on that long, brilliant series of biological experiments which were to culminate in his triumphant proof of the germ-causation of so many diseases of man and animals. In the early 1860's, Pasteur studied butyric fermentation and, much to his surprise, discovered that the butyric ferment, which is responsible for the bad odor in rancid butter, was a motile vibrio, a bacterial cell, in contrast to the non-motile plant (yeast) cells which he had found to be the cause of lactic and alcoholic fermentation. He writes:

> But, by a strange phenomenon, those infusory animalculae live and multiply indefinitely without requiring the least quantity of air. And not only do they live without air, but air actually kills them. It is sufficient to send a current of atmospheric air during an hour or two through the liquor where those vibriones were multiplying to cause them all to perish and thus to arrest butyric fermentation, whilst a current of pure carbonic acid gas passing through that same liquid hindered them in no way.

Afterwards, Pasteur called those micro-organisms which do not require, and are even inhibited by atmospheric air, anaerobes.

Now, also, is Pasteur engaged (1859–1864) in his classic series of experiments to

disprove Pouchet's assertions in regard to spontaneous generation. A year before starting discussion, Pasteur writes to Pouchet:

> I think you are wrong, not in believing in spontaneous generation (for it is difficult in such a case not to have a preconceived idea), but in affirming the existence of spontaneous generation. *In experimental science it is always a mistake not to doubt when facts do not compel affirmation.*

After a year's study, Pasteur came to the conclusion that the germs which developed in Pouchet's flasks came from the air. "Impossible!" retorted Pouchet. Pasteur had studied the atmospheric air by aspirating a current of air into a tube through a little plug of cotton wool. He had found that such filtered air did not cause growth in a tube containing culture media, but if a small fragment of this cotton wool through which air had been drawn was dropped into a tube of sterile media, prompt growth of microorganisms took place, due to germs and spores deposited on the filter. Then, because objection was raised on the ground that the cotton wool was an organic substance, Pasteur substituted for it asbestos fiber, a mineral substance, with the same results. Then Pasteur invented little glass flasks with long, curved necks; he found that if these flasks were filled with sterile media no

growth occurred, because the germs from the air were deposited in the curve of the flask's neck and there remained, without touching the liquid. But if the liquid in the flask was tilted up so as to wash into it some dust which had collected on the neck, then microorganisms developed in the media. Pasteur went further, literally and figuratively. During his vacation, in August and September of 1860, he set out, armed with seventy-three glass flasks with which to test the air on heights and in places far from habitation. As Valery Radot[91] so graphically remarks:

> Pasteur started for Arbois, taking with him seventy-three flasks; he opened twenty of them not very far from his father's tannery, on the road to Dole, along an old road, now a path, which leads to the mount of the Bergere. The vine labourers who passed him wondered what this holiday tourist could be doing with all those little phials; no one suspected that he was penetrating one of nature's greatest secrets. "What would you have?" merrily said his old friend Jules Vercel; "it amuses him!"

Of these twenty flasks which he opened, and then carefully sealed, eight showed growth. Then on through France he went and up into the Alps, where on the glacier Mer de Glace, above Chamonix, he exposed to the air twenty flasks, all but one of which remained sterile. In speaking of this

journey twenty years later, Pasteur said: "If all the results are compared that I have obtained until now, it seems to me that it can be affirmed that the dusts suspended in atmospheric air are the exclusive origin, the necessary condition of life in infusions."

In the summer of 1863, Pouchet and two associates, Joly and Musset, decided to repeat Pasteur's experiments. So, armed with four phials containing a hay infusion, they climbed to a narrow crevasse at the foot of one of the greatest glaciers of the Maladetta, 3000 meters above sea-level, where they opened, and then carefully sealed their flasks. Triumphantly, they asserted that all their flasks showed growth. Discussion waxed so warm that the Academy of Sciences, at the solicitation of Joly and Musset, appointed a Commission, before which the scientific adversaries could wage their battle of experiments. So, on April 7, 1864, before a brilliant audience at the Sorbonne, for not only scientists, but the public as well, were admitted, Pasteur met the objections advanced by Pouchet, detailed his own experiments, and, amid enthusiastic acclaim, really sounded the death knell of the theory of spontaneous generation.

Now Pasteur returns to his study of wines, and in January 1864, he announces to the Acadèmie des Sciences: "I have indeed reached this result that the alter-

ations (diseases) of wine are co-existent with the presence and multiplication of microscopic vegetations." Moreover, he found that keeping wine at a temperature of 50° to 60°c. for a few minutes killed these harmful germs, and thereby prevented the wine from becoming bitter, sour or "ropy." (See his Études sur le vin, Paris, 1866.)

The next year, 1865, marks the definite orientation of Pasteur's scientific energies into pathology and medical bacteriology. For from then until 1870, he devoted the major portion of his time to a study of pebrine, an epidemic disease of silkworms that was raging in such terrible proportions that it threatened to ruin the silkworm industry of France, and to flacherie, another disease of silkworms.[92] He demonstrated the contagious nature of pebrine and showed that contagion occurred either directly from infected to healthy silkworms on the same frame, or through soiling of the silkworm's food by the very infectious excreta of the diseased worms; in addition, Pasteur worked out a rather simple method for preventing the spread of the infection. Moreover, he showed that the "corpuscle," or germ, of pebrine is transmitted in the eggs of infected female worms.

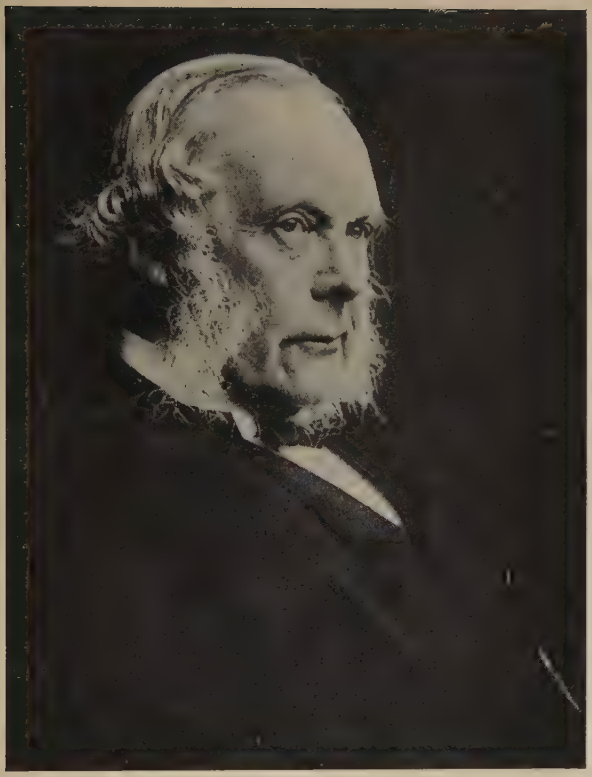
During this period of his researches, on October 19, 1868, at the age of forty-six years, Pasteur suffered an alarming cerebral hemorrhage, which caused a paralysis

of the entire left side of his body. "I am sorry to die," he said, "I wanted to do much more for my country." After a few months of convalescence, he was once more haunting his laboratory. New discoveries were fermenting in his brain; he was forever saying: "We must get to work!" Yet discoveries which he had already made were even now beginning to revolutionize medical and surgical practice. Joseph Lister (1827–1912), the Scotch surgeon whose greatest scientific contribution was the introduction of aseptic methods into surgery, frankly acknowledged his debt to Pasteur in an address which he gave before the British Medical Association in Dublin in 1867.

> When it had been shown by the researches of Pasteur that the septic property of the atmosphere depended, not on oxygen or any gaseous constituent, but on minute organisms suspended in it, which owed their energy to their vitality, it occurred to me that decomposition in the injured part might be avoided without excluding the air, by applying as a dressing some material capable of destroying the life of the floating particles.

And in 1892, at the Pasteur jubilee, Lister rendered in public, and in person, his homage to Pasteur, the results of whose researches Lister had been the first to put into practical application.

The material Lister employed was carbolic acid, which was used not alone for



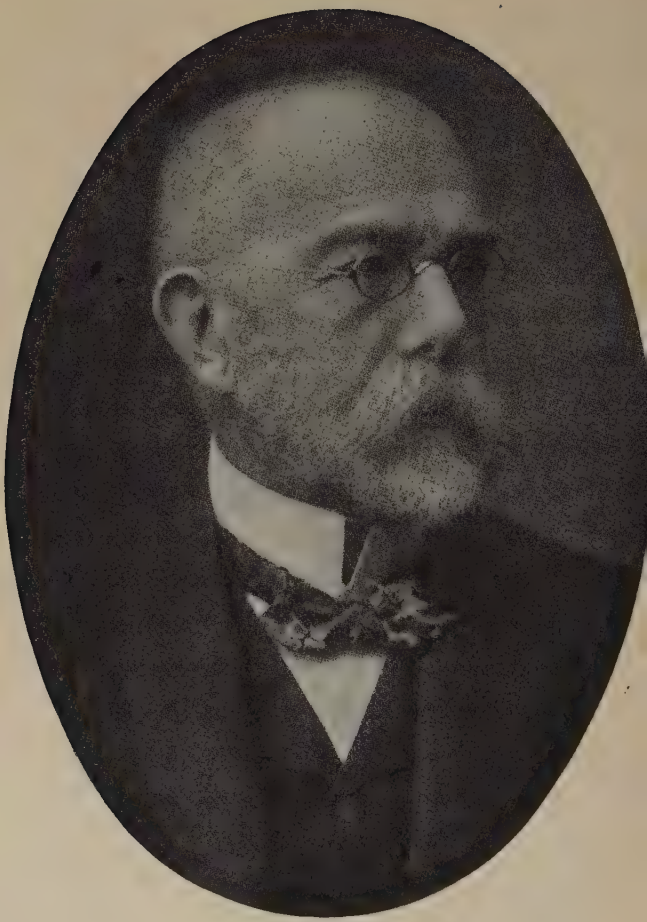
Lord Lister.
(1827–1912)

disinfecting the surgical instruments, sponges, etc., but was used on the operator's hands; during the whole course of the operation, a vaporizer of carbolic solution sprayed the atmosphere over and around the wound, and after the operation was over, the wound was again washed with the carbolic solution.

From now on, until his death in 1895, Pasteur's researches were largely devoted to problems relating to the cure and prevention of disease. It is interesting to note, however, that his later discoveries, which represent his supreme service to mankind and which did so much to bring to light the actual bacterial causes of various plagues and pestilences and fevers which for so many generations had scourged the human race, followed logically and almost inevitably from his earlier studies. Particularly is this true of his studies upon the nature of fermentation, and the coincident knowledge which he had gained of the morphology and physiology of microorganisms.

One of the first animal, and secondarily human, diseases which Pasteur studied was anthrax. The bacterial cause of this disease, Bacillus anthracis, was discovered in 1849 by Pollender, and in 1850 by Davaine, in the blood of cattle suffering with anthrax. In 1853 Delafond showed that the disease could experimentally be transmitted to healthy cattle by the

injection of anthrax blood which contained the bacterium. It was not, however, until July 1876, that a young country physician in Wollstein, Germany, Robert Koch (1843–1910) by name, published his classical article on anthrax.[93] In this communication, he reported having worked out the complete life-history of the anthrax bacillus, and in it he showed that the nature and distribution of the disease could be fully explained by the mode of development of the causative microorganisms, particularly their sporulation. This alone was a great contribution, this proof of sporulation by the anthrax bacillus and this complete elucidation of its life cycle. But there was still more! Koch reported that he had grown the anthrax bacillus in pure culture, unmixed with bacteria of any other kind, by employing hanging drops of aqueous humor and sterile blood serum placed over hollow ground slides; and by the use of pure cultures grown for a number of generations outside of the infected animal body he reported that he had produced anthrax in mice, guinea pigs and rabbits. A monumental piece of scientific investigation, this; for the first time in the history of the world a disease producing bacterium had been artificially grown in a pure state outside of the infected animal body, and the specific disease produced in healthy, different animals by injecting a pure



Robert Koch.
(1843–1910)

culture of the bacterium into their bodies. In November 1877, Koch[94] published a second paper in which he described his method of making smears of bacteria on cover-slips, fixing them by drying or gentle heat, and staining them with aniline dyes, which Weigert previously had employed for the demonstration of bacteria in tissues. In addition, he described a method for staining the flagella of bacteria.

Koch's studies led Pasteur to a study of anthrax and other infectious diseases to which, as Pasteur himself said at the time, "I have thus far been a stranger." Pasteur confirmed Koch's findings, and then went on to study another septicemic disease, known as malignant edema, a disease common to man and domestic animals, with the resultant discovery, in 1877, of the Vibrion septique, an obligate anaerobe.[95] In this same year, Patrick Manson (1844–1922), "the father of tropical medicine," discovered the phenomenon of filarial periodicity in the circulating blood of man; while four years earlier, in 1873, Obermeier[96] had demonstrated the Spirochaeta recurrentis in the blood of patients in the febrile stages of relapsing fever.

In 1879 Pasteur began his studies on chicken cholera, a disastrous disease of the chicken yard; this year was further signalized by Hansen's (1841–1912) discovery of B. leprae[97] in leprous nodules

and Neisser's (1855–1916) discovery of the gonococcus in gonorrheal secretions.[98]

The year 1880 was a memorable one. Eberth (1835–1926) discovered B. typhosus,[99] the cause of typhoid fever; Laveran[100] (1845–1922), while working at the Military Hospital of Constantine in Algeria discovered the Plasmodium malariae, the cause of malaria; and in the same year Sternberg[101] (1838–1915) and Pasteur[102] independently discovered the pneumococcus. Moreover, it was in 1880 that Pasteur[103] laid the cornerstone of the science of immunology by his discovery of protective vaccination against chicken cholera, a discovery, incidentally, which arose from a purely accidental occurrence. Pasteur had made some cultures of the bacillus of chicken cholera; then he was called away from the laboratory for several months. On his return, he found that his cultures, which had been standing on his desk for several months at room temperature and without transplantation, no longer killed healthy chickens upon injection, as previously they had done. Now they gave rise only to localized, non-fatal lesions. From this observation, Pasteur developed a method of protective vaccination against chicken cholera, by injecting first a *premier vaccin* of a very much attenuated or weakened culture of the microorganism, followed after twelve or fourteen days by a second, less attenuated culture (*deuxième vaccin*).

This was followed, in 1881, by Pasteur's clear-cut demonstration that anthrax vaccine is effective in the immunization of cattle against anthrax, or splenic fever. In this instance, he prepared his vaccine from a culture grown in a shallow layer of neutral chicken broth, the bacilli being attenuated, and spore formation prevented, by growth at 42–43°c. As Adami once said: "That a plague of diarrhea in a poultry yard, studied by a professor of chemistry, should be the seed from which has grown the vast development of later years is a strange fact, but fact, nevertheless."

In 1881, Koch[104] described his greatest technical achievement, the discovery of the pour-plate method for the isolation of bacteria in pure culture. Up to this time, no certain method had been available for obtaining pure cultures of microorganisms from mixtures. Koch employed nutrient gelatin in such proportions as to give a semisolid medium when cooled. To obtain pure cultures, he advised direct inoculation of the previously melted and then cooled gelatin, shaking it well to separate the individual cells, and then pouring of the gelatin over the surface of a sterilized glass dish.

Now that Koch had supplied correct methods for the recognition and cultivation of the exciting agents of infectious diseases, discoveries came "as easily as ripe apples fall from the tree," as Koch himself

expressed it. In 1882, Koch[105] reported his discovery of the tubercle bacillus, the cause of tuberculosis; in the same year Friedrich Löffler[106] (1852–1915), one of Koch's students and associates, discovered B. mallei, the cause of glanders.

The full account of Koch's experiments and deductions upon tuberculosis was not published until 1884.[107] It was in this communication that Koch first formulated in print the famous postulates known by his name, postulates which should be fulfilled before a given bacterium can positively be regarded as the cause of a given disease. Briefly, Koch's Postulates are: (1) the parasite must be found in every case of the disease, and under conditions which explain the pathology and clinical behavior of the disease; (2) the parasite must not be found as an accidental harmless invader in other diseases, and (3) a pure culture of the parasite, when introduced into the body of another animal, should be recovered from the diseased tissues of the experimentally infected animal. In this same communication, Koch published two ideas which later he had to withdraw: (1) that the small, refractile bodies found in the tubercle bacillus are spores, and (2) that tuberculosis of man and animals is identical, and is caused by an identical bacillus. It was not until 1898 that Theobald Smith[108] made the first

clear differentiation between the bovine and human types of tubercle bacilli.

In 1883 Koch[109] discovered the cholera vibrio, the cause of Asiatic cholera, thus pointing the way to quarantine and control of this deadly scourge of the tropics. This work was done while Koch was the head of the German Cholera Commission, first in Egypt and later in India. In 1884, Löffler[110] isolated in pure culture, B. diphtheriae, the cause of diphtheria, first seen by Klebs[111] one year earlier.

At this time (1884) Madame Pasteur wrote to one of her children: "Your father is absorbed in his thoughts; talks little, sleeps little, rises at dawn and, in one word, continues the life I began with him this day thirty-five years ago." In 1885, in collaboration with Chamberland, Roux and Thuillier, appeared Pasteur's[112] crowning discovery of preventive vaccination against hydrophobia. This resulted in the formal opening of the Pasteur Institute in Paris on November 14, 1888, contributions to which had poured in from all over the world. In the Institute, which Pasteur entered weary and ill, he remained as director until his death on September 28, 1895.

In 1885, Nicolaier[113] discovered B. tetani, and four years later Kitasato[114] first cultivated this microorganism in pure culture. In 1887, Weichselbaum[115] first cultivated the meningococcus in pure culture, and in

the same year Bruce[116] first described B. melitensis, the cause of Malta fever.

In 1892, William Henry Welch[117] (1850–) discovered the Staphylococcus epidermidis albus and its relation to wound infection (stitch abscess). In the same year, he and Nuttall[118] discovered the Bacillus aerogenes capsulatus (Welch bacillus), and in 1900[119] he grouped the pathological conditions caused by this bacillus. In 1891 and 1892, Welch and Flexner,[120] simultaneously with von Behring, described the pathological changes which follow the experimental injection of diphtheria toxin.

Coincident with the demonstration that in many of the infectious diseases the pathogenic or disease-producing agents are specific bacteria, it was a natural development of the science of bacteriology that attention should be centered upon the mechanism by means of which bacteria incite destructive changes in the body, as well as upon the methods by means of which the body combats bacterial invasion. A tremendous stimulus to this quest was afforded in 1888 by two of Pasteur's pupils, Emile Roux and Alexandre Yersin,[121] who made the amazing discovery that if the diphtheria bacillus is grown in broth, and the broth filtered, the bacterium-free fluid is not alone highly toxic, but the toxin is specific, because the injection of this fluid into an experimental animal such as a guinea pig sets up in the animal the

characteristic lesions of diphtheria. At almost the same time, Kitasato[122] discovered the presence of a specific toxin in a broth culture of the tetanus bacillus, from which the bacteria had been removed by filtration. In 1890, Behring (1854–1917) and Kitasato,[123] working in Koch's Institute, made their classical discovery that the blood serum of rabbits immunized with tetanus toxin developed antitoxic properties, *i.e.* the blood serum developed the capacity to so neutralize tetanus toxin that amounts of toxin which ordinarily would prove fatal could now be injected into such animals with impunity. Moreover, if such an immunized animal was bled, and its blood serum injected into another animal, this second animal would likewise be protected against tetanus toxin. Almost simultaneously, Behring[124] and his associates discovered diphtheria antitoxin, and in 1894 diphtheria antitoxin was introduced as a therapeutic agent in the treatment of diphtheria in man.

It soon became evident that diphtheria and tetanus constitute a group of rather special diseases, whose symptoms can experimentally be reproduced by the soluble, poisonous products (exotoxins) of the causative microorganisms, and in which immunity is due to the development of specific anti-substances (antitoxins) capable of neutralizing the toxins. The majority of infectious diseases do not fall

in this class; the agencies by which most pathogenic bacteria incite disease is through their endotoxins, poisons closely bound up with and contained within the bacterial cells, and against which antitoxins are not elaborated by the infected animal body. It was the research of Pfeiffer on cholera in 1891 which lead to a differentiation of exotoxins and endotoxins.[125]

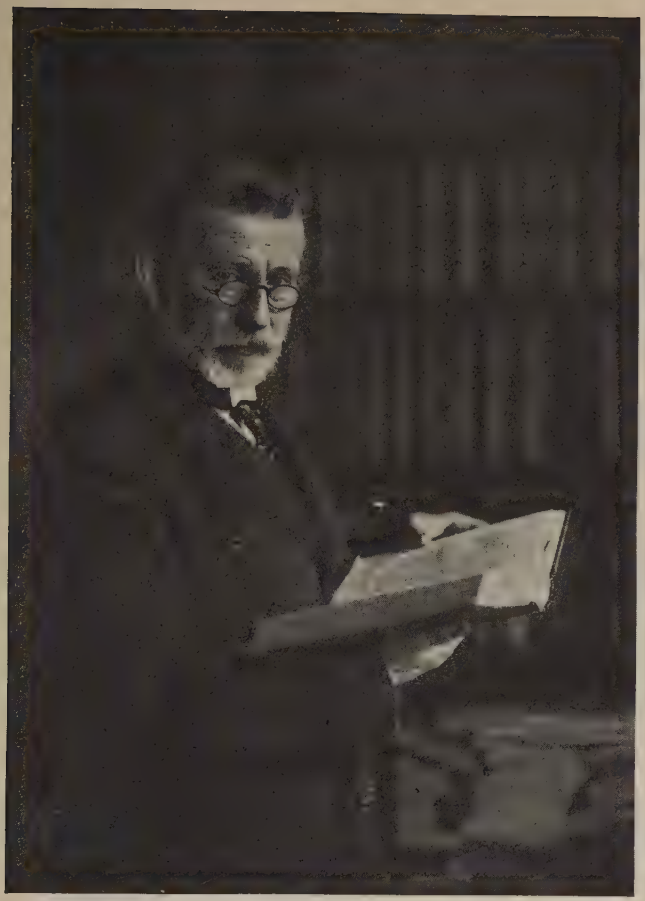
In spite of the fact that no antitoxic defence is manifested by the body against most bacterial invaders, it soon was discovered that the body does exhibit a humoral (body-fluid) defence, not alone against the bacterial poisons but against the bacteria themselves. John Hunter, Traube and Lister had all observed the anti-putrefactive action of shed blood and body fluids, but apparently Grohman, in 1884, was the first experimentally to demonstrate that fresh blood plasma has an inhibitory effect upon bacterial growth. In 1888, Flügge and Nuttall[126] actually demonstrated under the microscope the destruction of such bacteria as B. anthracis by the defibrinated blood, as well as by the pericardial and pleuritic fluids, of rabbits, mice, sheep, dogs and pigeons. In 1889, Buchner[127] still further narrowed the search by showing that this antibacterial property of the blood resides in the blood serum; to the bactericidal substances in the blood he gave the

name alexins (to ward off, or protect). In 1894, Pfeiffer[128] announced his discovery that if cholera vibrios are injected into the peritoneal cavity of an immunized guinea pig, the bacteria quickly lose their motility, swell, become granular and finally dissolve (Pfeiffer's reaction). Not alone did he demonstrate that cholera vibrios do not undergo such dissolution when injected into the peritoneal cavity of a normal, non-immune animal, but he also showed that if a little blood serum from a cholera immune guinea pig is injected along with cholera vibrios into the peritoneal cavity of a normal animal, dissolution of the bacteria does take place.

Following this discovery by Pfeiffer of the lysogenic or bacteriolytic property of an immune serum, it was found that this reaction also occurred in a test tube with fresh, immune serum, but that on standing, or on heating the serum to 56°c. for half an hour, the bacteriolytic power of the serum was destroyed. However, if to this heated immune serum was added fresh, normal serum from the same animal or from another species of animal, the vibrio-dissolving power of the serum was restored. In other words, there are two components in a cholera-immune serum, both of which are necessary before the bacteriolysis characteristic of Pfeiffer's reaction can occur. Further analysis of this phenomenon at the hands of Bordet,[129]

Ehrlich and Morgenroth,[130] and Metchnikoff brought out the close resemblance between a bacteriolytic immune serum and a hemolytic immune serum, the latter prepared by immunizing an animal against alien red blood corpuscles, just as the former is prepared by immunizing an animal against a bacterium, such as the cholera vibrio. Bordet found, by a series of classical experiments, that the thermolabile (heat-sensitive) constituent of both hemolytic and bacteriolytic immune serum, which he called the "substance bactericide" was the same, and he identified it with Buchner's "alexin" and Ehrlich and Morgenroth's "complement." The thermostable (heat-resistant) component of bacteriolytic and hemolytic immune serum was called by Bordet "substance sensibilisatrice," a component of serum synonymous with Ehrlich's "amboceptor" or "immune body." The subsequent work of Bordet and Gengou[131] on the reaction of "complement fixation" found practical diagnostic application later in such tests as the Wassermann reaction, a serological method for the diagnosis of syphilis devised in 1906 by August Wassermann (1866–1925).

Almost coincident with Pfeiffer's discovery that certain bacterial invasions of the animal body incite the body to the production of specific bacteriolytic substances which can be demonstrated in the circulating blood, Gruber and Durham[132]



Paul Ehrlich.
(1854–1915)

discovered another product of bacterial invasion of the animal body, to which the name agglutinin has been given. They noted that if the blood serum of an animal immunized against B. typhosus be added to a homogeneous suspension of typhoid bacilli, the previously cloudy fluid clears and the bacilli are clumped at the bottom in a coherent, viscid mass, i.e. the bacteria are agglutinated; cholera vibrios mixed with typhoid antiserum are unaffected. It was Widal[133] who in 1896, first gave this discovery of agglutinins a practical diagnostic application, by showing that the blood serum of a patient suffering from typhoid fever, when mixed with typhoid bacilli, will specifically agglutinate these bacilli, thereby affording a test by means of which it can be determined whether a given patient is suffering from a typhoid infection or not. This test is generally known as the "Widal reaction," or better the "Gruber-Widal reaction." Since Gruber's and Widal's pioneer researches, the agglutination test has proved of immense value in the clinical study not only of typhoid fever, but of other infectious diseases such as the paratyphoid fevers, typhus fever, Malta fever and dysentery. In 1897, Kraus[134] discovered precipitins in serum, substances closely allied in nature to agglutinins. He found that if he mixed a clear filtrate of a typhoid bacillus culture with typhoid antiserum, a specific cloudiness or pre-

cipitate appeared in the tube. The same phenomenon occurred if a plague bacillus filtrate was mixed with plague antiserum or if a cholera vibrio filtrate was added to cholera antiserum. In each instance the reaction was specific, i.e. no clouding occurred if, for example, a typhoid bacillus filtrate was mixed with plague antiserum, or with cholera antiserum. In the hands of Ascoli, Bordet, Nuttall and others, it was found that the precipitin test not only could be practically applied in the diagnosis of certain diseases, such as glanders and anthrax, but that its use could be extended still wider for the identification of animal and plant proteins. And it was Uhlenhuth who showed that the test had a wide medicolegal use, especially in the identification of human blood.

All of these detailed discoveries turned the scientific spotlight upon the fluid elements of the body. They showed that, in many bacterial diseases, combative substances such as antitoxins and bacteriolysins could be demonstrated in the blood, whose action was directed either against poisonous products of the invading bacteria, or against the bacteria themselves. Out of these discoveries arose the Humoral Theory of Immunity, a modified return to the ancient teachings of Hippocrates, in which the proper concentration of defensive substances in the humors of the body was substituted for the proper

concentration of bile and mucus, as constituting the mechanism by means of which contagious diseases are prevented or cured. But already a rival Cellular Theory of Immunity was finding vociferous scientific adherents. The attempt to prove that the major defence of the body against bacterial invasion resides in the cellular elements of the blood stream and of the tissues really dates from the early studies of Metchnikoff[135] (1845–1916) in which he showed the immense importance of the leucocytes (white cells) of the blood in freeing the body of pathogenic bacteria. This result, he demonstrated, is brought about by the fact that leucocytes move by throwing out protoplasmic processes which are able to engulf, and then destroy by a process of digestion, foreign bodies such as bacteria. To such cells he gave the name "phagocytes" (to eat cells), and the process by which bacteria, and other foreign substances, are engulfed he called "phagocytosis." At the hands of Metchnikoff and his students a further differentiation of phagocytes into "wandering cells" and "fixed tissue cells" was made; the rôle of phagocytosis in such infections as anthrax, tuberculosis, cholera, gonorrhea and staphylococcus and streptococcus infections was elaborated upon. Metchnikoff's fundamental studies upon phagocytosis were soon amplified by test-tube experiments performed in 1895 by Denys

and Leclef.[136] They showed that if leucocytes and streptococcus-immune serum and streptococci are mixed, the increased phagocytosis, as evidenced by the greater number of streptococci engulfed by the leucocytes, is due to substances in the immune serum which act upon the bacteria and make them more readily ingested. Still later, in 1903, Wright and Douglas[137] proposed the term "opsonin" (I prepare food for) for the thermolabile substances in fresh, normal serum and in immune serum, which act upon bacteria and make them more susceptible to phagocytosis. Now that a certain degree of convergence between the opposing "humoral" and cellular" theories had been demonstrated, Ehrlich[138] (1854–1915) attempted to unite the diverse phenomena of the two systems into one great theory; out of this attempt he developed his "Side Chain" Theory of Immunity.

While the battle over the mechanism of immunity was being waged, fundamental discoveries regarding certain protozoon diseases were being made. In 1889, Theobald Smith[139] demonstrated the parasite of Texas Fever, Pyrosoma bigeminum. In 1893, Theobald Smith (1859–), the great American comparative pathologist and bacteriologist, immortalized himself by giving to the world the first scientific proof that an arthropod (a tick) may serve as a carrier of a protozoon disease. In that

year, Smith and Kilborne[140] published the results of researches conducted from 1889–1892 upon an infectious disease of cattle, variously known as Texas fever, redwater or piroplasmosis, in which they showed that the disease is due to a protozoon parasite, Piroplasma bigeminum, which is transmitted by ticks of the genus Boophilus. This brilliant discovery paved the way for that classical series of investigations upon insect carriers of disease, which culminated in the triumphant proof that malaria and yellow fever are mosquito-borne, which in turn pointed the way to the control of these ancient scourges of the human race.

As early as 1894, the year in which Yersin[141] and Kitasato[142] independently isolated B. pestis, the bacterial incitant of bubonic plague, Patrick Manson formulated his fertile theory that malaria is a mosquito-borne disease. He laid special stress upon the phenomenon of "ex-flagellation" exhibited by the malaria parasite in drawn human blood, and showed Ronald Ross (1857–) that this phenomenon pointed directly to a further development of the parasite in a blood-sucking insect.[143] He convinced Ross that he should work out the problem in India after giving him, as Ross himself wrote in 1900, "a chain of reasoning from which it was impossible to escape." This led to Ross observing ex-flagellation take place

in the body of the mosquito (1895); in 1897–98 he saw crescent-derived, pigment-bearing parasites in the gut-wall of Anopheles mosquitoes. Thereafter, he followed out the complete cycle of development of the malaria parasite (Plasmodium), thus scientifically establishing the fact that certain mosquitoes are the living carriers by means of which malaria is spread from man to man.

Sir Almroth E. Wright proved the practicability and efficacy of typhoid vaccination by his inoculation of the entire British forces in the South African war, and his vaccination of 3000 soldiers in India between 1898 and 1900.

From our rapid review of the nineteenth century, certain deductions and generalizations can be drawn. We have seen how the first half of the century was chiefly occupied with solidifying, and enlarging medical knowledge of the pathology and clinical nature of infectious diseases. Through the genius of Laënnec, who developed the stethescope in 1817, an instrument was put into the hands of medical science by means of which the telltale cries and hidden whispers locked within the diseased human body were made audible to the ear of the examining physician. A magic door of diagnosis was opened; a really objective examination of certain organs, particularly those of the chest, was now for the first time made possible. We have seen how,

following Laënnec, brilliant Schools of Medicine arose in France, Germany, in Austria, in England, in Ireland, in America. Then Virchow came upon the scene, to direct the science of Pathology into cellular channels, and to indelibly imprint his genius upon that science. And yet, in a review of the period from 1800 to 1850, one fact stands out with dazzling clarity. *There was no knowledge of how infectious diseases actually were caused!* Medical science was awaiting its liberator, and that man was coming in the person of a chemist, Pasteur.

Almost upon the hour of the close of the first half of the nineteenth century the recently perfected microscope began to point the way. For it was in 1850, that Davaine announced his discovery of a bacillus in the blood of cattle suffering from a deadly disease known as anthrax; and three years later Delafond pointed out that there was an intimate relationship between certain bacteria in the blood of cattle and the disease anthrax. He found that if he took normal cattle blood and injected it into a healthy cow, no disease resulted. Moreover, if he took the blood of an anthrax infected cow and injected this blood into a healthy animal, anthrax did not develop *if the injected blood contained no anthrax bacilli.* But when the blood contained anthrax bacilli, such blood

was infective when injected into healthy cattle.

In the further unfolding of the development of Bacteriology, we have watched the orderly sequences of Pasteur's researches. We found him, as a young man, at his chemical, and physico-chemical, studies; then we saw him attack the ancient dogma of spontaneous generation, and prove its fallacy. Then, beginning in 1864 and extending through 1870, came Pasteur's studies of diseases of wines, and then his researches upon an epidemic disease of silk-worms. Now, stimulated and directed by Robert Koch's classical work upon anthrax, published in 1876 and 1877, we find Pasteur embarking upon that strangely fruitful series of studies of animal and human diseases, out of which were laid the strong, broad foundations of Bacteriology as a science, as well as of Immunology.

From 1880, we witnessed how the last twenty years of the nineteenth century recorded an almost breath-taking series of bacteriological discoveries. In the seclusion of laboratories, in the wards of hospitals, in field and in camp, disease after disease yielded the secret of its bacterial causation. Great plagues and pestilences that had swept the world for uncounted centuries, bubonic plague, cholera, tuberculosis, typhoid, and a long list of other infectious diseases, were now found to be caused by definite, distinct

and recognizable bacteria, whose mode of spread was now subject to study, and the products of whose life activities could be analyzed. Out of the researches upon the modes of spread of various infectious diseases developed the science of Epidemiology; out of the study of bacterial products developed vaccines and sera and the broad science of Immunology. What new discoveries were awaiting the advent of the twentieth century?

CHAPTER V

THE TWENTIETH CENTURY

In 1900, the United States Army Commission on Yellow Fever was formed, consisting of Walter Reed, James Carroll, Aristides Agramonte, and Jesse W. Lazear; of this Commission Walter Reed (1851–1902) was president and, according to General Leonard Wood, "the originating, directing and controlling mind." The Commission, which commenced its investigations in Cuba in August, 1900, first began a series of experiments in which mosquitoes, chiefly of the species Stegomyia, were allowed first to feed upon the blood of yellow fever patients, and then, later, the same insects were made to feed upon normal, non-immune individuals. The first nine human experiments were negative; but the tenth, in which Carroll was the voluntary subject, was successful. Four days after being bitten by an infected yellow fever mosquito, Carroll developed a severe attack of yellow fever, from the effects of which he died a few years later. On September 13, Lazear, at work in the yellow fever wards, observed a Stegomyia alight upon his hand. Deliberately, Lazear watched the mosquito drink its fill of his blood. Five days later, he became violently ill with yellow fever and, after a short illness, died. The results obtained by the

Commission[144] can briefly be summarized as follows: Yellow fever is naturally acquired by the bite of one species of mosquito only, the Stegomyia fasciata, and then only if the mosquito has sucked the blood of a yellow fever patient during the first four or five days of the disease. An incubation period of at least twelve days is required, after the mosquito has had its meal of infected blood, before the mosquito becomes infective i.e. capable of transmitting yellow fever to a susceptible individual, by biting. Of the scientific findings of this Commission Professor W. H. Welch wrote in a letter to the Secretary of War of the United States: "they constitute one of the most valuable contributions to medicine and public hygiene which have ever been made in this country, with the exception of anesthesia." Speedy confirmation of the Commission's conclusions followed, and William Crawford Gorgas (1854–1920) immortalized himself by putting into practical application in Panama the principles of mosquito control, which have led to the virtual conquering of malaria and yellow fever on the Isthmus.

In 1905, Schaudinn[145] (1871–1906) capped his brief and brillant career by his discovery of Treponema pallidum, the cause of syphilis. Earlier fundamental contributions of Schaudinn include the working out of the life cycle of certain coccidia, and the tracing of the different stages in

the development of the malaria parasite in human red blood corpuscles. In 1906, August von Wassermann (1866–1925) published his method of serum diagnosis of syphilis,[146] a test known as the Wassermann test. In 1910, Paul Ehrlich and Hatta introduced salvarsan, popularly known as 606, for the treatment of syphilis. The next year, 1911, witnessed the first successful cultivation of the Treponema pallidum outside of the body; this was accomplished by Hideyo Noguchi,[147] who so recently fell a martyr to yellow fever in Africa.

In 1912, McCoy[148] and Chapin first cultivated B. tularense from a disease of ground squirrels in California, known as tularemia. This disease, which resembles bubonic plague in rodents, was first described in 1911 by McCoy.[149] The first two instances of tularemia in the human were described in 1914 by Wherry[150] and Lamb, and the disease has since been extensively studied by Francis and Simpson.

In 1911,[151] Bass first cultivated on artificial culture media the malarial parasite, discovered thirty-one years earlier by Laveran.

In 1913,[152] Schick introduced his toxin test for immunity to diphtheria, a procedure generally known as the Schick Test.

In 1915, Twort,[153] during the course of an unsuccessful attempt to cultivate vaccine virus, discovered the bacteriophage

phenomenon, or transmissible lysis of bacteria, since studied intensively by d'Herelle,[154] and often referred to as the Twort-d'Herelle phenomenon.

The year 1923 was signalized by Dr. & Mrs. Dick's[155] experimental demonstration that hemolytic streptococci are the causative bacterial factor in scarlet fever, a discovery which has opened the way for the prevention and control of this disease.

In 1924, Calmette[156] reported upon the use of his vaccine, known as B. C. G. (Bacille bilié Calmette-Guerin), and its application in children as a prophylactic agent against tuberculosis.

In conclusion, it should be noted that a considerable number of highly infectious diseases of both man and animals have been found to be caused by what are known as filterable viruses.[157] As early as 1898, Löffler and Frosch,[158] while studying foot-and-mouth disease, a highly contagious disease of cattle, which also is transmissible to man, made the astonishing discovery that the virus of this disease is able to pass through the pores of such fine porcelain filters as will hold back visible bacteria. They took lymph from an infected animal and filtered it, and they found this filtered lymph to be bacteria-free, so far as recognizable bacteria were concerned. Yet as small an amount as 0.02 c.c. of such filtered lymph was capable of inciting, on injection, foot-and-mouth disease in a healthy cow.

From this artificially infected animal they transferred the infection to six successive animals, and it was estimated that the sixth calf, in the series, received less than one two-billionth of the original lymph. Because of the experimentally determined fact that one fifty-thousandth part of the original lymph was not infective, Löffler and Frosch drew the justifiable conclusion that the filter-passing virus of foot-and-mouth disease must be an invisible, but living, microorganism capable of multiplication. Since 1898, almost fifty diseases of man, animals and plants have been demonstrated to be caused by filterable viruses; among a few of the more common virus diseases of man are small pox, rabies or hydrophobia, epidemic infantile paralysis, and probably the common cold.

In our consideration of Jenner, it was noted that probably the first observation of allergy in an acute, infectious disease was made by Jenner in 1798, during the course of his clinical and experimental studies of smallpox. It is a curious fact that it was exactly one hundred years later, namely in 1898, that the fundamental observations on hypersensitiveness were made, upon which are based our present knowledge of allergy and anaphylaxis. The researches of Pasteur, and others, upon the general subject of vaccination, had abundantly confirmed the fact that when an animal previously injected with an antigenic

substance, such as bacterial protein or other proteins, is subsequently reinjected with the same antigen, a certain degree of immunity, or protection, is established in the animal. In 1898, Hericourt and Richet[159] found that repeated injections of eel serum into dogs gave rise in these animals to an increased susceptibility to this substance, rather than to an immunity. To this anomolous phenomenon of hyper-susceptibility Richet first applied the term "anaphylaxis" (ἀνά, against or without, and Φυλαξις, protection) to distinguish it from prophylaxis, or protection. Later, from 1902 to 1908, Portier and Richet[160] continued their studies, using extracts of the tentacles of certain sea anemones, Actinia. The substance which they extracted, actinocongestin, was found to be highly toxic, doses of 0.042 grams per kilogram causing diarrhea, vomiting, collapse, and death in dogs. If a considerably smaller dose than this was given a dog, the animal suffered only a temporary illness; then if, after several days' interval, a second injection of less than one quarter or one fifth of the ordinary lethal dose was given, rapid and severe symptoms developed in the dog, often followed by death. These experiments left little doubt that the first injection gave rise to a marked, increased susceptibility in dogs to the poison used.

Now, at the instigation of Richet, Arthus[161] turned his attention to the effect of injection of normally harmless substances, such as milk and horse serum; he found that results similar to those obtained by Richet followed the injection of such non-toxic substances. He showed that if he injected rabbits at definite intervals with normal horse serum, a substance in itself harmless to normal rabbits, the first two or three injections were absorbed, and gave rise to no symptoms. But subsequent injections of the same horse serum, given subcutaneously, led to increasingly severe local reactions. This is the Arthus Phenomenon. If the animals were first injected subcutaneously, and later intravenously or intraperitoneally, serious symptoms, such as dyspnea, convulsions, and even death supervened. Arthus, at this time, discovered the specificity of anaphylaxis; as he himself wrote: "the rabbit sensitized by and for serum is not so for milk, and vice versa."

Soon after diphtheria antitoxin was discovered it was noted that, occasionally, the injection of antitoxin into human beings gave rise, after an incubation period of from three to ten days, to exanthematous eruptions, urticaria, swelling of the lymph glands, and often albuminuria and mild pulmonary symptoms. Then the medical profession was shocked by the sudden death of a healthy child of an

eminent German professor following a prophylactic injection of diphtheria antitoxin. It was early recognized that such untoward happenings were not attributable to the antitoxin in the horse serum, but depended upon some other constituents or properties of the serum. In 1902, von Pirquet began his study of these peculiar clinical reactions, his first case being a child in Escherich's clinic who was given an initial injection of horse serum, followed ten days later by a second injection of the same material. On the same day, the child developed a rash and symptoms of fever. From his initial studies, von Pirquet[162] propounded his theory that the incubation period of a disease represents the interval between the entrance into the body of the inciting microorganism and the formation of antibodies by the invaded host; symptoms of the disease only manifest themselves when the inciting microorganisms have been altered by antibodies.

Later, in conjunction with Schick, von Pirquet[163] in the course of his studies upon the effects produced by the injection and re-injection of horse serum, coined the term "serum sickness" to describe the train of symptoms which followed such injections. They noted that serum sickness may sometimes arise in individuals injected with serum for the first time, and they ascribed this to some peculiar predisposi-

tion or idiosyncrasy on the part of such individuals. They noted, however, that in those persons injected with serum a second time, after intervals of weeks or even months, the symptoms frequently were more severe, more rapid in development, and tended to occur with greater regularity. In the case of individuals who manifested symptoms following a single injection, they suggested that such immediate reactivity possessed diagnostic import, as implying that a previous infection had occurred. It was during these studies that von Pirquet coined the term "allergy" (ἄλλος, altered, and ἔργον, energy or reactivity) to signify that condition of altered susceptibility which causes an individual to react to a second inoculation of an antigen in a manner different from his reaction to the first inoculation.

During the time that von Pirquet and Schick were pursuing their studies in Germany, Theobald Smith[164] in the United States described a phenomenon in guinea pigs which was quite similar to that observed by Arthus two years earlier in rabbits. In the course of standardizing diphtheria antitoxin, Smith observed that guinea pigs injected with diphtheria toxin-antitoxin mixtures developed rapid and alarming symptoms if they were injected subcutaneously with normal horse serum after a short interval. The animals exhibited marked restlessness, itching of the

skin, and violent convulsions; within half an hour fully 50 per cent of the animals were dead.

The above detailed researches of Richet, Arthus, von Pirquet and Schick, and Theobald Smith established the fundamental facts concerning hyper-susceptibility upon which our present-day knowledge of the subject is based. Following these pioneers, came the studies of Otto in Germany, and Rosenau and Anderson in the United States, as well as Vaughan and Wheeler, and Novy, studies which helped to buttress known facts and which developed new ideas and facts, as well.

And now, with a brief backward look along the road we have come, and a briefer glance into the mist that veils the future, we will bring our story to a close. In the course of our short, and necessarily rapid, review of the historical development of the ideas held by medical men concerning infectious diseases, we have observed that the growth of man's knowledge has not been one of unbroken progression. At any given period old errors have been carried over, along with new accretions of fact. If this be true of medical knowledge how much more has it been true of the ideas of disease held by the ordinary, untrained man who, by his inevitable limitations, must always lag behind the scientific procession.

We have seen how, from early prehistoric man until less than two thousand years ago, disease was thought of almost solely in terms of magic, and treatment of disease was largely a matter of ritual. With the advent of the Hippocratic influence, disease was first stripped of its magical trappings, and a successful attempt was made to dissociate medicine from religion and philosophy. After a period of lapse of several hundred years, we have seen how Galen, during the second century A.D., restored and refurbished the Hippocratic doctrines of disease, doctrines which held almost undisputed sway until the sixteenth century and the advent of Paracelsus. But Paracelsus, that strange medical Don Quixote of the Renaissance, while tilting his lance against Galen, reintroduced the magical element into the theory of disease which he elaborated. To that extent, Paracelsus retarded, rather than advanced, the long intellectual battle that medical men had waged in their endeavor to come at a true understanding of the nature of infectious diseases. We have seen how, in the same century, Fracastor ventured a curiously prophetic guess in regard to the causation of contagious maladies; but it was merely a guess, unsupported by experimental facts.

From the sixteenth century, up until the middle of the nineteenth century, we have been a witness to the amazing

fact that the development of man's ideas of infectious disease followed along the lines of an increasingly detailed study of symptoms and bodily lesions, but not of basic causes. In the furtherance of this development, certain pioneers in various branches of science during the sixteenth and seventeenth centuries made monumental contributions, Vesalius in Anatomy, Paré in Surgery, Harvey in Physiology, Malpighi and van Leeuwenhoek in Microscopy. And yet the basic groundwork of knowledge of the human body had not been sufficiently laid, and experimental methods had not been sufficiently elaborated, to make possible a reasoned understanding of disease processes. As evidence of this, we have followed the rise of the Theoretical Systemmatists of the seventeenth and eighteenth centuries, who erected their elaborate, and often ingenious, theories of disease upon the shaky scaffolding of incomplete and one-sided knowledge. Through these centuries, we have seen how the controversy over the theory of spontaneous generation stirred scientific circles, and how it was continued up into the nineteenth century.

In the eighteenth century, with the advent of Morgagni and Bichat, we witnessed the rise of modern Pathology; with the appearance of Jenner we traced the scientific beginnings of Immunology But not until the nineteenth century,

with its elaboration of instruments of scientific precision, and the increasing development of the experimental method of approach, did there occur a scientific orientation of man's ideas of infectious diseases. In bringing this to pass, three scientific giants towered above all others; Virchow, the father of Cellular Pathology, Darwin, the Naturalist, and Pasteur, the father of Bacteriology.

With the blossoming of the experimental genius of Pasteur during the latter half of the nineteenth century, and the momentous discoveries activated by his genius, we were a witness of the most profound revolution in man's concepts of infectious diseases that the world has ever known. Now, for the first time, we find science speaking of diseases in terms of their exciting bacterial cause; for vague generalizing are now substituted tangible, recognizable, microscopic agents of disease, whose life processes and the products of whose activity are subject to observational and experimental study in the laboratory. As the nineteenth century drew towards its close, and on up into the twentieth century, the number of infectious diseases caused by proven, specific microorganisms widened and widened, until today we find that there is only a comparatively limited number of diseases in this category whose exciting etiology is unknown. Coincident with these revolutionary accessions

of scientific knowledge of causes, there occurred equally revolutionary developments in the matter of diagnosis, prevention and treatment of infectious diseases. Thus, we have witnessed the fact that modern Medicine has especially stressed prevention of infectious diseases; not content with waiting until disease manifests itself, it has attempted to dry up and eradicate the sources of infection, and the channels by which it is spread. Coincident with this, we have witnessed the development of vaccination and serum therapy; the rise of accurate bacteriological and serological methods of diagnosis; the discovery of such tests as the Schick Test, by means of which susceptibility to diphtheria can be ascertained, thereby admitting of immunization of individuals susceptible to this disease.

Out of all this welter of recent and revolutionary scientific development, certain hard-won facts have triumphantly emerged. It is a fact, for example, that malaria and yellow fever are insect-borne diseases, and that if the mosquitoes, which transmit these diseases, are eradicated, the diseases will be eradicated. It is a fact that preventive vaccination against smallpox has made this ghastly scourge of the human race a medical curiosity in communities where vaccination is rigidly enforced. It is a fact that early and adequate administration of diphtheria anti-

toxin has shorn diphtheria, that former nemesis of childhood and adult life, of the major part of its terrors. It is a fact that typhoid fever, a disease which felled one out of every seven American soldiers during the Spanish American War, and which killed more American troops than did Spanish bullets, is also a disease capable of almost complete control in any community, where strict supervision is practiced over the three F's of its transmission, fingers, flies, food, and where prophylactic typhoid vaccination is enforced.

Epochal as have been the advances made in the past eighty years, there are still great gaps in our knowledge of the true nature of most infectious diseases. In the case of certain important infectious diseases, such as the common cold and influenza, not even the exciting agent is positively known; and in neither of these diseases does medical science possess clean-cut, definite methods of prevention or treatment. In the science of Immunology, particularly, there are many basic foundation stones still missing in the already formidable structure of our knowledge. But that is one of the heartening things about modern Science; nothing remains static. Old, accepted theories will have to be modified in the light of new discoveries; there must inevitably be a re-vamping, and re-orienting of concepts as the inquir-

ing minds of men push back farther and farther the boundaries of the unknown. Duclaux once said: "It is because science is sure of nothing that it is always advancing." And you will remember Minot's words: "We have enthroned science in the imagination, but we have crowned her with modesty, for she is at once the reality of human power and the personification of human fallibility."

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INDEX OF PERSONAL NAMES

Adami, 192
Adams, 155
Addison, 155
Aesculapius, 22
Agramonte, Aristides, 211
Ali Abbas, 51, 52
Allbutt, 55
Anderson, 220
Andral, Gabriel, 154, 161
Aretaeus (the Cappodician), 39
Aristotle, 22, 32, 33, 34, 52, 112
Arthus, 217, 219, 220
Asclepiades, 35, 36, 37
Ascoli, 203
Auenbrugger, Leopold, 140
Avicenna, 50, 51, 52, 65, 86, 87

Bacon, Roger, 57, 58, 59, 60, 62, 100
de Baillou, Guillaume, 84
Bass, 213
Bassi, Agostino, 163
Beaumont, 126
von Behring, 196, 197
Bernard, Claude, 162
Bersot, Ernest, 129
Berzelius, 172, 180
Bichat, Marie-François-Xavier, 140, 142, 143, 144, 159, 222
Boerhaave, Hermann, 134, 136
du Bois-Reymond, 158
de Boot, Arnold, 111
Bordet, 199, 200, 203
Borelli, 106, 107
Boyle, Robert, 131
Bretonneau, Pierre, 154
Bright, 155
Brown, John, 138, 139
Brown, Sir Thomas, 113
Bruce, 196
Buchner, 198, 200
Buffon, 123, 125
Buonanni, 113

Caelius Aurelianus, 36, 38, 39
Calmette, 214
Calvin, v, 77
Carlyle, 35
de Carpi, Berengarius, 74
Carroll, James, 211
Chamberland, 195
Chapin, 213
Charles IX, 79
Cheyne, George, 134, 155
Pope Clement IV, 58
Clowes, William, 84
Cober, Tobias, 111
Cole, William, 134
Corrigan, 155
Corvisart, 151
Cullen, William, 137, 138
Cumston, 36

Darwin, Charles Robert, 151, 169, 171, 172, 223
Darwin, Francis, 169
Davaine, 167, 188, 208
Dawson, 45, 47
Defoe, Daniel, 118, 119
Delafond, 167, 188, 208
Democritus, 22
Denys, 204
Desmazieres, 163
Dick, Dr. and Mrs., 214
de Diemerbroek, Isbrane, 111

Diocles, 34
Diodorus Siculus, 11
Dioxippus, 34
Douglas, 205
Duclaux, 177, 226
Dujardin, Felix, 167
Durham, 200
von Dusch, 165, 167

Eberth, 192
Ehrenberg, 165, 166
Ehrlich, Paul, 200, 205, 213
Emerson, 35
Empedocles, 26
Epicurus, 35
Erasistratus, 34
Escherich, 218
Euripides, 21, 32
Eustachius, 77

Fallopius, 61, 77
Fioravanti, 61
Flexner, 196
Flügge, 198
Fontana, 132
Ford, 166
Fossel, Victor, 72
Fothergill, John, 140
Fracastor, 62, 69, 71, 72, 73, 83, 84, 90, 221
Francis, 213
Francis II, 79
Freind, John, 134
Frerichs, 158
Frosch, 214, 215

Galen, XI, 35, 39, 40, 42, 43, 44, 49, 52, 55, 56, 63, 65, 74, 76, 77, 84, 89, 92, 93, 108, 221
Galileo, 93
Garrison, 54
Geber, 52, 53
Gengou, 200
Gerhard, 155
Giardia, 100
Glisson, Francis, 111
Goodsir, 167
Gorgas, William Crawford, 212
Graves, 155
Greenwood, Major, 110
Grew, 94, 95
Gruber, 200, 202

Hahnemann, Samuel, 138, 139, 140
von Haller, Albrecht, 138
Hansen, 191
Harvey, 74, 89, 90, 92, 93, 95, 100, 102, 148, 222
Hatta, 213
Heine, Heinrich, 61
Heller, 162
Helmholtz, 158, 162
Henle, 158, 166
Henry II, 79
Henry III, 79
Herakleitos, 20
Heraclides, 22
d'Herelle, 214
Hericourt, 216
Herodicus, 22
Heroditus, 11, 12, 14, 32
Herophilus, 34
Hippocrates, 1, 20, 22, 24, 25, 27–32, 34, 35, 37, 38, 40, 42, 45, 49, 56, 65, 105, 136, 203
Hodges, Nathaniel, 112
Hoffmann, Friedrich, 136, 137
Holmes, Oliver Wendell, 166
Homer, 20
Hooke, 94, 95
Hunter, John, 146, 198
Hunter, William, 74
Huxham, John, 140

Ibu al Khatib, 55
Im-hotep, 8

Janssen(s) (the), 132
Jastrow, 13
Jayne, 12
Jefferson, Thomas, 148
Jenner, Edward, 140, 144, 146, 147, 148, 215, 222
Job, v
Joly, 184
Justinian, v

Keats, v
Kelly, Dr. Howard, 82
Kilborne, 206
Kircher, 94
Kitasato, 195, 197, 206
Klebs, 12, 14, 18, 19, 195
Knutsson, Bengt, 85
Koch, Robert, x, 166, 189, 191, 193, 194, 195, 209
Kraus, 202
Kutzing, 163

Laënnec, Réné Théophile Hyacinthe, 152, 154, 207, 208
Lamb, 213
Lancisi Giovanni Maria, 130
Latour, 163, 172
Laveran, 192, 213
Lazear, Jesse W., 211
Leclef, 205
Le Clerc, 6
van Leeuwenhoek, 94, 95, 97, 98, 99, 100, 101, 102, 107, 116, 130, 163, 222
Le Sage, 120
Liebig, 173, 180
Linnaeus, 131
Lister, Joseph, 43, 57, 186, 198
Locke, John, 108
Löffler, Friedrich, 194, 195, 214, 215
Louis, 154

Mac Callum, 95
Magendie, 155
Mahomet, 49
Malpighi, 92, 94–97, 222
Manson, Patrick, 191, 206
Maria Theresa, 123
Maspero, 9
McCoy, 213
Mead, Richard, 132, 134
Mercuriali, Hieronymo, 71
Metchnikoff, 200, 204
Minot, 226
Molière, 118
Molyneux, William, 108
Monardi, 60
Mondeville, 57
Montague, Lady, 144
Montaigne, 14
Moodie, Roy L., 2, 5
Morgagni, Giovanni Battista, 140, 141, 142, 222
Morgenroth, 200
Moses, 18
Müller, Otto Friedrich, 132
Musset, 184

Napoleon, v
Needham, 117, 123, 125, 127, 128, 164
Neisser, 192
Newton, 132
Nicolaier, 195
Noguchi, Hideyo, 213
Novy, 220
Nuttall, 100, 196, 198, 203

Obermeier, 191
Oliver, Dr., xii
Osler, 104
Otto, 220

Paracelsus, 53, 57, 60, 62, 63, 65, 66, 68, 83, 84, 104, 108, 139, 221

Paré, Ambroise, 62, 79, 81, 82, 83, 84, 222
Pasteur Louis, x, 43, 130, 148, 151, 172, 175, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 188, 191, 192, 193, 195, 196, 209, 215, 223
Payne, 111
Peter of Maricourt, 59
Petronius, 34
Pfeiffer, 198, 199, 200
Phipps, James, 146
von Pirquet, 218, 219, 220
Pitcairne, Archibald, 134
Plato, 22, 32
Plenciz, 130, 131
Pliny, 112
Pollender, 167, 188
Pope Clement IV, 58
Portier, 216
Pouchet, 173, 174, 175, 182, 184
Prascianus, 53
Priestley, 129, 164
Pringle, John, 140

Radot, Valery, 183
Read, 45
Reade, Charles, 24
Redi, Francesco, 113, 114, 115, 116, 126
Reed, Walter, 211
Reinhardt, 159
Remak, 158
Renault, Bernard, 2, 4, 5
Rhazes, 50, 51, 52
Richet, 216, 217
Roger, 57
Rokitansky, 155
Roland, 57
Rosenau, 220
Ross, Alexander, V, 113
Ross, Ronald, 206
Roux, Emile, 195, 196
Ruffer, Sir Marc Armand, 9

de Sauvages, François Boissier, 137, 152
Schaudinn, 212
Schick, 213, 218, 219, 220
Schopenhauer, V
Schroeder, 165, 167
Schulze, Franz, 164, 165
Schwann, Theodor, 158, 163, 164, 165
Semmelweiss, 167
Sennert, Daniel, 111
Servetus, 77
Simpson, 213
Singer, 29, 101
Skoda, 155
Smith, Theobold, 194, 205, 206, 219, 220
Socrates, 32
Sophocles, 32
Soranus (of Ephesus), 22, 38, 39
Spallanzani, Lazzaro, 123, 126, 127, 128, 129, 164
Spieghel, 111
Stahl, George, 136, 137
Sternberg, 192
Stokes, 155
Strabo, 33
Sudhoff, 15
Susruta, 17
de Suzzi, Mondino, 74
Swammerdam, Jan, 94, 95, 96, 97, 116
Swift, 100
Sydenham, Thomas, 107, 108, 109, 110, 111, 118, 136, 137, 140, 141
Sylvius, 77, 104–106

Themison, 37
Theodoric, 57

Thessalus, 37, 38
Thucydides, 29, 39
Thuillier, 195
Traube, 158, 198
Trommer, 162
Turpin, 163
Twort, 213
Tyndell, 164

Uhlenhuth, 203

Vallisnieri, 116
Van Helmont, 102, 103, 112
Vaughn, 220
Vercel, Jules, 183
Vesalius, 40, 62, 74, 76, 79, 83, 84, 89, 95, 222
Vierordt, 162
da Vinci, Leonardo, 40, 74
Virchow, Rudolf, 2, 3, 151, 158, 159, 161, 208, 223
Voltaire, 129

Walcott, 3
Wassermann, August, 200, 213
Weichselbaum, 195
Weigert, 191
Welch, William Henry, 196, 212
Wheeler, 220
Wherry, 213
Widal, 200
Willis, Thomas, 112, 117
Wood, General Leonard, 211
Wright, Sir Almroth E., 205, 207
Wunderlich, 158

Yersin, Alexandre, 196, 206

Zipporah, 18
Zoroaster, 17

INDEX OF SUBJECTS

Acupuncture among Chinese, 45
Acute diseases, types of, 38
Adjuvants, use of, by Egyptians, to psychotheraphy, 11
Agglutinin, 202
Alchemy as forerunner of chemistry, 52
Alexins, 199
Allergy, 215, 216, 219
Amulet, oldest form of prophylaxis against disease, 10
Anaphylaxis, 215, 216, 217
Anatomical drawing from nature substituted for schematic representations of organs and structures, 74
  researches, 84
Anatomie générale, 143
Anatomy of vegetables, 95
  knowledge of, in Talmud, 19
  morbid, study of, 141
Anemia, Egyptian, 12
Animalcula Infusoria, 132
Animism, doctrine of, 103
Anthrax, 188
  bacillus, 167
  Koch's articles on, 189, 191
  Pasteur's study, 191
Antibacterial property of blood, 198
Antiquity of disease, 1, 2
Antitoxin, 197
Apology, 79
Aqua regia, discovery of, 53
Arabic medicine, medieval period and renaissance, 49–88
Arcana, 67
Arsenic made by Paracelsus, 68
Arthritis deformans, vi, 3
  in ancient Egypt, 10
Arthropod as carrier of protozoon disease, 205
Arthus Phenomenon, 217
Arts of prehistoric men as precursors of ancient Egyptian civilization, 8
Asepsit, pioneer, 82, 83
Atomic or corpuscular theory of disease, 35, 36
Atoms, doctrine of, 22, 24
Autopsies performed by Hebrews, 19

Bacillus aerogenes capsulatus (Welch bacillus), 196
anthrax, 167
diptheriae isolated in pure culture, 195
lepidophagus, 5
leprae, discovery of, 191
mallei, discovery of, 194
melitensis, 196
tetani, discovery of, 195
tubercle, discovery of, 194
typhosus, discovery of, 192
Bacteria, existence of, methods of gaining knowledge of, 3
first description of, 97
mechanism of, 196
in petrified feces of fishes and reptiles, 4
in pure culture, pour-plate method for isolation of, 193
Bacteriology, beginning of science of, 166
medical, Pasteur's studies in, 185
Bears, cave, of Pleistocene period, vi
Beginnings of art of medicine, 8
of philosophy, 8
Bilharzia hematobia in Egyptian mummies, 10
Biological contributions of Aristotle, 33, 34
Black art, in Egypt, 12
death, v, 61
Blood, circulation of, 89
solution of fundamental physiological problem, 92
Body, as curative agent, 83
humors, as taught by Galen, 42, 43
Bones, fossil, 2
Breathing, difference between intercostal and diaphragmatic, 42
Brunonian system, 138
Bubonic plague, 85
correlation of with mice, recognized in Biblical times, 18

Canals, semicircular, discovery of by Eustachius, 77
Capillary channels, 92
connection between arteries and veins, 100
Caseous degeneration, known by ancient Hebrews, 19
Causation of disease, pore constriction and pore relaxation, 38
Cave gout, 3

Cell(s), red blood, first description of, 100
yeast, discovery of, 163
Cellular pathology, 159, 160
rival theory of immunity, 204
Cerebri Anatome, 112
Charms and amulets as prophylactic procedure, 8
Chemistry, derivation of, 11
developments in, 162
Cholera vibrio, discovery of, 195
Chronic diseases, 39
Circulation of blood, 89
and Galen, 40, 41
pulmonary, discovery of, 77
Classification of temperaments, Galenic, 43
Clinical inspection and observation, 25
medicine and Arabs, 49
observation, progress in, 107–112
Clinician, first great experimental, 40
Code Hammruabi, 15
sanitary, of Jewish people, 19
Complement fixation, 200
Concept(s) of insect pests among Hebrews, 19
of nature of disease processes, contributions to, 62
rudimentary, of nature of disease, 1
Contagion, classification of, 83
Contagionum vivum theory of disease, 130, 131
Contagious maladies, cause of, as taught by Fracastor, 71
Contagiousness of leprosy and variola, recognized by Avicenna, 52
Continuation of Facts and Observations Relative to Variolae Vascinae, or Cow Pox, 147
Contributions, original, of Paré, to surgery and obstetrics, 81
Conservation of energy, theory of, 26
Coprolites, 4
Cretenism and endemic goiter, correlation between established, 68
Cure of disease in Babylonia and Assyria, 13

De Fabrica Humani Corporis, 74
De Febribus, 112
De Formatione Pulli in Ovo, 96
Demonstration of falsity of doctrine of spontaneous generation, 114

Dental caries, 2
De Ovo Incubato, 96
De Peste, 111
De Pulmonibus, 96
De Sedibus et Causis Morbarum per Anatomen Indagatis, 141
Developments in pathology and chemistry, 162
De Viscerum Structura, 96
Diagnosis, change in, 152
Diaphoretics, use of, by Egyptians, 11
Die Einheitshestrebungen in der wissenschaftlichen Medizin, 158
Differentiation of exotoxins and endotoxins, 198
Discoveries of micrococci, 3
  of new diseases, 154
  of nitric acid, sulphuric acid and aqua regia, 53
Disease (s), v, vi
  acute, types of, 38
  animistic theory of, 136
  antiquity of, 1, 2
  atomic or corpuscular theory of, 35, 36
  as biological factor, xi
  causation of, pore constriction and pore relaxation, 38
  cause of, investigated by microscope, 94
  chronic, 39
  contagionum vivum theory of, 130, 131
  contagious, doctrine of *contagio animata* as cause of, 94
  cure of, in Babylonia and Assyria, 13
  discoveries of, 154
  division of, into two classes, 37
  epidemic, infectiousness of, 28
  etiologic agents of, 52
  as expression of wrath of God in old Testament, 18
  as functional disorder of viscus, 46
  germ theory of, 166
  Hippocratic theory of, 26
  infectious, 83
    flies as possible transmitters of, 82
    nature of, 69
    passage of from one person to another, 29
  insect carriers of, 206
  in Iranian religion, 17
  as manifestation of power of supernatural being, among Aryans of ancient India, 16
  miasmas as cause of, 28

Disease (s), miner's (occupation), 68
modern germ theory of, forerunner of, 69
and Fracastor, 71
origin and development, 2
Egyptian, 10
primitive concepts of, 7
processes, nature of, 84
proof of germ—causation of, 181
as punishment, in early period of Greece, 20, 21
as taught by Paracelsus, 67
as visitation of malignant spirits, 25
Dissection (s), human, 62
of muscles, 44
and relation of to knowledge of anatomy, physiology and pathology, 27, 28
Vesalius' and effect on former theories, 76
Dissociation of medicine from priestcraft and philosophy, 27
Diuretics, use of, by Egyptians, 11
Doctrine of atoms, 22
of *contagio animata* as cause of contagious disease, 94
Drug(s), metasyncritic, 38
specific, 39
Dry cupping among Chinese, 45

Ebers Papyrus, 12
Eighteenth century, 123
Emancipator of Medicine, 27
Embryology, descriptive, father of, 95, 96
Emetics, use of, by Egyptians, 11
Empiric school of medicine, 37
Endotoxins, differentiated from exotoxins, 198
Enemata, use of, by Egyptians, 11
Epidemics, v
cause of, Galenic, 44
diseases, infectiousness of, 28
knowledge of nature of, among Greeks and Romans, 29
Epidemiologist, first great, 110
Epilepsy, 26
as sacred disease, 27
Esperienze Intorno alla Generazione degl' Insetti, 114
Essai d'hematologie, pathologique, 161
sur les Maladies et les Lesions Organiques du Coeur et des Gros Vaisseux, 151

Etiologic agents of disease, 52
Etiology of acute eruptive fevers, 50
Eustachian tube, 77
Evidence of accurate observation among primitive peoples, 14
Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus, 89
Exotoxins, differentiated from endotoxins, 198
Experiments concerning spontaneous generation, 123, 125, 126, 127, 128, 129

Fees, physician's, in ancient Babylonia, 15
Fermentation and causation of disease, 131
Fever(s), etiology of acute eruptive, 50
typhus, first good scientific description of, 69
Filterable viruses as cause of large number of infectious diseases, 214
First Lines of Practice of Physic, 138
Flies as possible transmitters of infectious diseases, 82
Fossil remains, 2
Foundations of present day Chinese physiology and psychology, 46
Fracture, 2
Further Observations on Variolae Vaccinae, or Cow Pox, 147

Galenic dogma of "laudable pus" contradicted, 57
Generation, spontaneous, 164, 165, 172–184
Germ-causation of disease, proof of, 181
theory of disease, 166
Geschichte der Medizin, 158
Gil Blas, 120
Glands, imbalance of, v
Goiter, endemic, and cretenism, 68
Gonococcus, discovery of, 192
Gonorrhea as initial stage of syphilis, 68

Harvey's contributions, 92, 93
Healing gods in ancient Iran, 17
of Babylonians, 13
Hematology, studies leading to foundation of, 162
Hemolytic streptococci, causative bacterial factor in scarlet fever, 214
Hippocrates' concepts of disease, 29, 30, 31, 32
Hippocratic Oath, 24

Hippocratic Oath, system of medicine, 26
theory of disease, 26
Histology, founder of, 95
Homeopathy, father of, 139
Humoral pathology, 29
theory of immunity, 203
and Islamic physicians, 49
Hydrophobia, discovery of preventive vaccination against, 195

Iatrochemical school, 104, 105
founder of, 105
Iatromathematicists, 132, 134, 136
Iatrophysical school, 106
founder of, 106
Idea of Philosophical History of Plants, 95
Immunity, humoral theory of, 203
rival cellular theory of, 204
"Side Chain" theory, 205
Immunology, beginnings of science of, 192
Infection(s), v, vi
affinities of, 73
by means of fomites, 73
theory of, extended, 39
from water, 28
Infectious disease(s), cause of, 83
passage of from one person to another, 29
Infectiousness of epidemic diseases, 28
Inoculation against smallpox, 144
preventive, against smallpox, practiced by ancient Chinese, 45
Inquiry into Causes and Effects of Variolae Vaccinae, or Cow Pox, 147
Insect carriers of disease, 206
Inspection, regulated, of meat destined for sacrifices, in ancient Egypt, 12
Instinctive hygienic lore, 6
Introduction of aseptic methods into surgery, 186
Inventum novum, 140
Iron made by Paracelsus, 68

Journal of Plague Year, 118

Kidney, atrophy and abscess of, known to ancient Hebrews, 19
Koch's postulates, 194

Laudanum (opium) made by Paracelsus, 68
Lead made by Paracelsus, 68
Leprosy, contagiousness of, 52
Lesions, vi
  pathological, 2
Ligaments, round, discovery of, by Eustachius, 77
Ligation, use of, in surgical operations, 79
Liver, cirrhosis and necrosis of, known to ancient Hebrews, 19
Luneburger Chronik, 61
Lungs, structure of, 96
  tumors of, known by ancient Hebrews, 19
Lysogenic property of immune serum, 199

Malaria, v
  description of, by Susruta, 17
Malpighian bodies, 96
Massage among Chinese, 45
Measles described by Rhazes, 50
Mechanical Account of Poisons, 132
Mechanism by which bacteria incite destructive changes in body, discovery of, 196
Medical sects, 38
Medicine in Brahmanical period, 16
  dissociated from religion and philosophy, 25
  Greek, before Hippocrates, 22
  Hippocratic, 26
Meningococcus, 195
Mercury made by Paracelsus, 68
Metasyncrisis, 38
Methodic school of medicine, 37
Methodism, 38
Methods, new, introduced into clinical medicine, 161, 162
Miasmas as cause of disease, 28
Micrococci lepidophagus, 4
Micrographia, 95
Microscope, 92
  compound, invention of, 95
  further improvements in, 163
Microscopic channels, 92
Microscopists, pioneer, 93, 94, 95, 96, 97, 98, 99, 100, 101
Midwives, professional, among Hebrews, 18
Mohammedan practice, 54
Morbid processes, essence of bodily alterations, 35

Nature of infectious diseases, man's ideas of, vi
Nerves, difference between motor and sensory, 42
trigeminal, auditory and glossopharyngeal, discovery of, by Eustachius, 77
Nineteenth century, 150–210
Nitric acid, discovery of, 53
Nosologic methodica sistens morborum Classes, Genera et Species, 138
Nosology or Classification of Diseases, 138
Note on Vegetable and Animal Proto-organisms Spontaneously Generated in Artificial Air and Oxygen Gas, 173

On Contagiousness of Puerperal Fever, 167
Opsonin, 205
Origin of Species, 169
supernatural, of disease, in Babylonia and Assyria, 13
Osservaziono Intoino agli Animali Viventi che si trovano negli animali viventi, 114
Osteomyelitis, 2, 5
Ovaries, discovery of, by Eustachius, 77

Pandemics, medieval, 60
Parasitology, father of, 114
Parts of body, as taught by Galen, 42
Pasteur Institute, opening of, 195
Pathology, cellular, 159, 160
comparative, knowledge of, among Hebrews, 19
developments in, 162
humoral, 29
"naked eye," 142
Pasteur's studies in, 185
Personal hygiene in ancient Egypt, 11
Physician (s), distinct from priests among Hebrews, 18
earliest known, 8
fees in ancient Babylonia, 15
Islamic, and humoral theory, 49
and priest identical in ancient Egypt, 8
Plants, studies on microscopic structure of, 95
Plasmodium malariae, discovery of, 192
Pneumococcus, discovery of, 192
Pore theory of Asclepiades, 37
Potassium sulphate made by Paracelsus, 68
Pott's disease in Egyptian mummy, 9
Pour-plate method for isolation of bacteria in pure culture, 193

Power of Sun and Moon over Human Bodies, 134
Precipitin test, 203
Prehistoric horse, vi
  man to Hippocrates, 1–49
Preservation of micro-bacterial microorganisms, 34
Preventive vaccination against hydrophobia, discovery of, 195
Priest-physicians, 27
    identical in ancient Egypt, 8
Primitive concepts of disease, 7
  doctor and therapeutic procedures, 7, 8
  medicine man, 7
Prophylaxis, oldest form of, against disease, 10
  of plague as considered by Ibu al Khatib, 55
Protozoa, entozoic, first description of, 100
  parasitic, first description of, 100
Psychotherapy, Egyptian, 10
Puerperal convulsions, 26
Pulse feeling, art of, in China, 45
  study of, 62
Purgatives, use of, by Egyptians, 11
Putrefation, experiments on nature of, 94
Pyorrhea alveolaris, vi, 2
Pyrosoma bigeminum, 205

Researches, anatomical, 84
Rheumatism, differentiated from gout, 84
  first used in modern sense, 84
Rise of modern pathology, 140, 141, 142, 143

Salvarsan, introduced, 213
Sanskrit documents, 16
Sarcina ventriculi, discovery of, 167
Scarlet fever described by Rhazes, 50
Schick test, 213
School(s) of Alexandria, 34
  clinical, development of, 155, 158
  Empirc, 37
  German physiological, 158
  Methodic, 37
  Montpellier, 56
  Salerno, 56
Scientific beginning of immunology, 144, 145, 146, 147, 148, 149
Scrutinium pestis, 94

Serum sickness, 218
Seventeenth and eighteenth centuries, 89–149
Side Chain theory of immunity, 205
Signatures, 67
Smallpox described by Rhazes, 50
  in skin of Egyptian mummy, 10
Sorcery, belief in, 56
Sources of knowledge of early Hebrew medicine, 18
Staphylococcus epidermis albus, 196
Stereochemistry, science of arrangement of atoms, 177
Stethescope developed, 152
Study(ies) on chicken cholera, 191
  of pulse and examination of urine as basis of practical teaching, 62
St. Vitus dance, epidemic of, 61
Specialism in Egypt, noted by Herodotus, 11
Specificum purgans Paracelsi, 68
Spermatozoa, first description of, 100
Spondylitis in ancient Egypt, 10
Spontaneous generation, 112, 113, 114, 164, 165, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184
Sulphur made by Paracelsus, 68
Sulphuric acid, discovery of, 53
Suprarenal bodies, discovered by Eustachius, 77
Surgery, introduction of aseptic methods into, 186
  knowledge of, in the Talmud, 19
Surgical procedure in Bible, 18
Suppuration, prevention of, advocated by Mondeville, 57
Swamp Emanations and Their Cure, 130
Syphilis, clinical nature of, 71
  knowledge of advanced by Fracastor, 83
  sive de marbo gallico, 69
  as taught by Paracelsus, 68
  venereal nature of, 71

Talmud, as source-book of Jewish medicine, 19
Teachings of Epicurus, 35
Theoretical systematists, 102
Theory of conservation of energy, 26
Therapeutic(s) measures of Chinese, 45
  practical, 83
Theurgy, or magic basis of methods of healing of Phoenicians and other pagan Semites, 15

Thoracic duct, discovered by Eustachius, 77
Torula cerevisiae, 163
Tracheotomy, first mention of, 37
Traité de l'Auscultation Médiate, 152
des classes des Maladies, 138
Transmissibility of leprosy recognized by ancient Babylonians, 15
Treatise on Membranes, 143
Treatment of disease among Aryans of ancient India, 16
matter of ritual, 25
Treponema pallidum cause of syphilis, discovered, 212
Tubercle bacillus discovery of, 194
Tuberculosis, 26
Tularemia, 213
Tumors of lungs, known by ancient Hebrews, 19
Twentieth century, 211–226
Twort-d'Herelle phenomenon, 214

United States Army Commission on Yellow Fever, 211
Urine, examination of, 62
Uses of Liquids, 31
Uterus, first accurately described by Eustachius, 77

Vaccination, preventive, discovery of, against hydrophobia, 195
Variola, contagiousness of, 52
Variolation, 144
Vibriones, four species of, 166

Whooping cough, 84
Widal reaction, 202
Witch doctor, 7
Worm diseases recognized by ancient Egyptians, 12

Yellow fever, descriptive summary of, 212
United States Commission on, 211

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